National Eye Institute

Annual Report of Intramural

Research

October 1, 1988
to
September 30, 1989

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00135-17

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biochemistry of Retina and Pigmented Epithelium in Health and Disease

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI: Helen H. Hess M.D. Medical Officer (Research) OSD, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Office of the Director of Intramural Research, NEI

SECTION

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.3	1.0	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The effects of nutrition, oxidation, and other environmental factors (light intensity or darkness) on the incidence and progress of posterior subcapsular opacities (PSO) associated with retinal degeneration was studied in pink-eyed Royal College of Surgeons (RCS) rats, in which rod photoreceptor outer segment debris accumulates secondary to a phagocytic defect in retinal pigmented epithelium. There was evidence that oxidative changes in polyunsaturated fatty acids in debris led to water-soluble toxic aldehydes that were detectable in the vitreous and toxic to lens cells and membranes. Dystrophic rats fed a natural ingredient diet (NIH-07) were highly sensitive to retinal light damage, beginning at 1 to 4 foot-candle intensity; 27% of the rats developed mature cataracts by 7 to 12 months. Increased light intensity (cyclic or constant) increased the percentage of rats with mature cataracts, while rearing the rats in darkness from birth prevented PSO and mature cataracts. A purified diet (AIN-76A) fortified with 0.4% beta-carotene plus 0.01% BHT also prevented PSO and mature cataracts. Rhodopsin bleaching appears to be essential for retinal light damage and PSO. A 100% incidence of bilateral mature cataracts occurred in dystrophic rats exposed to 700 foot-candles of constant light for 48 hours at 22 to 28 days postnatal, the period when rhodopsin increased 70% in debris. A similar incidence of bilateral cataracts occurred in congenic control RCS rats given 18 days of dark adaptation to increase rhodopsin by 50%, followed by the same constant light exposure. In vitro, free retinaldehyde can act as a photosensitizer to generate singlet oxygen, an extremely energetic oxidant. Present results suggest a similar effect in vivo, with damage to both lipids and proteins. Antioxidants may slow or prevent cataracts in some human retinal diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00162-07 CB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Vitreous Fluorophotometry

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI: Monique S. Roy M.D. Visiting Scientist CB, NEI

COOPERATING UNITS *(if any)*
Biomedical Engineering and Instrumentation Branch, Division of Research Services, NIH (Peter Bungay, Ph.D.)

LAB/BRANCH
Clinical Branch

SECTION
Section on Retinal and Vitreal Diseases

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.4	0.4	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Vitreous fluorophotometry was performed in patients with diabetes mellitus without retinopathy, patients with diabetes mellitus with nonproliferative retinopathy, and normal volunteer subjects, age- and sex-matched to the patients. A new method for evaluating blood-retinal barrier permeability to fluorescein and diffusivity of fluorescein in the vitreous was developed. The amount of fluorescein leakage into the vitreous of patients was compared to that of the normal subjects. Correlations with other features of diabetes, such as the quality of diabetic control, the existence of subclinical neuropathy and nephropathy, and other complications were sought.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00198-06 CB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Sorbinil Retinopathy Trial

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Monique S. Roy	M.D.	Visiting Scientist	CB, NEI
Others:	James R. Carl	M.D.	Senior Staff Fellow	CB, NEI

COOPERATING UNITS *(if any)*
National Institute of Diabetes and Digestive and Kidney Diseases, NIH (R. Silverman)

LAB/BRANCH
Ophthalmic Genetics and Clinical Services Branch

SECTION
Section on Retinal and Vitreal Diseases

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.7	0.7	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Oral sorbinil, an aldose reductase inhibitor, was administered in a double-masked randomized trial to diabetics with no or minimal diabetic retinopathy. This was done to evaluate the effects of sorbinil on the development of diabetic retinopathy and to continue investigating the safety and toleration of sorbinil. The study is being conducted simultaneously in 10 research centers in the United States.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00217-04 LI

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Lymphocyte Migration in Experimental Autoimmune Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	Jeffrey N. Bloom	M.D.	Senior Staff Fellow	LI, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Clinical Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.26	0.26	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Experimental autoimmune uveitis (EAU) induced by immunization of rats and other experimental animals with S-antigen (a soluble antigen from the retina) is being investigated in this laboratory as a model of human intraocular inflammation. This experimental inflammation can be transferred from donor rats to naive recipients using lymphocytes harvested from the spleen or lymph nodes. Following harvest of the cells from the donors and 3 days in culture with stimulating antigen, the cells are injected into the intraperitoneal cavity and 5 to 7 days later the recipient rats develop EAU. The disease can also be transferred using a T-helper cell line by intraperitoneal or intraocular injection. The mechanism of transfer of disease is unclear. This work has used radioactive labeling to determine the fate of these lymphocytes after injection into the peritoneal cavity or blood during the development of uveitis. The goal of this project is to understand the initiating mechanisms of inflammation and to extend knowledge of these mechanisms to applications in human inflammations. Cells from an S-antigen-specific T-cell line migrate into the retina and cause EAU. The kinetics of this migration are being studied. S-antigen-specific cells reach the eye in greater numbers if the inflammation in the eye is induced by S-antigen than if it is induced by another mechanism.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00218-04 LI

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)
Acquired Immune Deficiency Syndrome

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI

COOPERATING UNITS *(if any)*
See next page

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Clinical Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.09	0.09	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Cytomegalovirus (CMV) retinitis is the major cause of blindness in AIDS patients. As we have previously shown, ganciclovir is effective in treating this infection, but the disease relapses without continued maintenance. Maintenance therapy requires intravenous infusion and is associated with marrow toxicity. A one-center trial of foscarnet in the therapy of CMV retinitis is under way.

Cooperating Units

Laboratory of Tumor Cell Biology, National Cancer Institute (S. Zaki Salahuddin, Ph.D.); Laboratory of Cellular and Molecular Biology, National Cancer Institute (Dharam Ablashi, D.V.M.); Department of Critical Care Medicine, Clinical Center (Henry Masur, M.D.); Laboratory of Tumor Cell Biology, National Cancer Institute (Robert C. Gallo, M.D.); Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases (H. Clifford Lane); Director, National Institute of Allergy and Infectious Diseases (Anthony S. Fauci, M.D.)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00219-04 LI

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Effect of Bromocriptine on Human Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	Janet L. Davis	M.D.	Senior Staff Fellow	LI, NEI
	David C. Herman	M.D.	Senior Staff Fellow	LI, NEI
	Jeffrey N. Bloom	M.D.	Senior Staff Fellow	LI, NEI

COOPERATING UNITS *(if any)*
Metabolism Branch, National Cancer Institute (Marie C. Gelato, M.D.)

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Clinical Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.91	0.91	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In recent years the literature has contained increasing evidence that pituitary hormones are capable of regulating the immune system. There is evidence to suggest that prolactin is an immunostimulatory hormone and that reduction of serum prolactin levels in experimental animals by hypophysectomy or treatment with bromocriptine will result in a degree of immunosuppression.

This information has been applied to humans, and two clinical studies have begun. Both are in early phases of patient recruitment. One study is a randomized trial comparing placebo and bromocriptine in recurrent anterior uveitis. Using as outcome the number of recurrences per year, the study will determine whether bromocriptine is capable of regulating the immune system in these patients. The second trial focuses on the additive effects of cyclosporine plus bromocriptine in attempts to treat patients with posterior uveitis at lower doses of cyclosporine to reduce renal toxicity while achieving immunosuppression. Cyclosporine and prolactin compete for binding sites on the lymphocyte.

Further studies will be designed to elucidate other aspects of the neuroendocrine axis that may be used to regulate the immune system in the treatment of autoimmune diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00220-04 LI

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Endocrine Modulation of Immune-Mediated Eye Disease in Rats

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	David C. Herman	M.D.	Staff Fellow	LI, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Clinical Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.31	0.31	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In recent years there has been increasing evidence that hormones are capable of regulating the immune system. It has been suggested that prolactin is an immunostimulatory hormone and that reduction of serum prolactin levels in experimental animals by hypophysectomy or treatment with bromocriptine will result in a degree of immunosuppression.

An animal model of experimental autoimmune uveitis (EAU) induced by immunization of rats with S-antigen (a soluble antigen from the retina) is used to study intraocular inflammatory disease. We have demonstrated a decrease in antibody production in both male and female rats and a decreased incidence of uveitis in female animals. No significant effect on the immune responses, as measured by lymphocyte proliferation, was seen. As reported before, high doses of cyclosporine (10 mg/kg) result in only partial reduction of intraocular inflammation. We have demonstrated that the suppression of prolactin by concurrent use of bromocriptine in combination with low-dose cyclosporine is more effective than either drug separately in suppressing both the incidence of disease and cellular and humoral immune responses. Evidence in the literature suggests that cyclosporine competes with prolactin for binding sites on lymphocytes. Reductions in prolactin level may reduce competition for those sites and make cyclosporine treatment more effective. Further studies with this animal model will elucidate other aspects of the neuroendocrine axis that may be used to regulate the immune system to treat autoimmune diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00221-04 LI

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Intraocular Class II Antigen Expression in Endotoxin-Induced Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	Horst Helbig	M.D.	Special Volunteer	LI, NEI
	Rebecca Gurley	M.S.	Biologist	LI, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Clinical Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.31	0.31	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Endotoxin is a polysaccharide derived from the cell wall of gram negative bacteria. When injected into the footpad or the eye of a rat, it will induce an inflammatory reaction within the eye. The mechanism of this inflammation is still unclear. However, since several types of anterior uveitis in humans appear to be linked to gram negative bacteria exposure, this is considered a relative model for anterior uveitis in humans such as occurs with Reiter's syndrome. In this study, the expression of class II antigens was studied within the eyes of rats receiving *Escherichia coli* endotoxin by immunohistochemical techniques. We observed that the expression of class II antigens on the ciliary body and iris preceded the influx of inflammatory cells into the eye and that the inflammatory cells that entered the eye were primarily neutrophils with some monocytes. No T-cells were present in the inflammatory infiltrate. The inflammatory cellular infiltrate could be inhibited by indomethacin or colchicine; however, this did not alter the expression of class II antigens by the iris or ciliary body indicating that this expression is not simply a consequence of the inflammatory infiltrate but may be intimately involved with the mechanism of the expression of endotoxin-induced uveitis. Corticosteroids were capable of suppressing both the cellular inflammatory infiltrate and the expression of class II antigens. The expression of class II antigens on nonlymphoid cells within the eye may be important in antigen presentation or may simply signal a phenotypic change on the cells due to the interaction of endotoxin with the cell membranes. The findings were compared with the expression of class II antigen in passive and active intraocular Arthus reaction. The effect of endotoxin on ocular inflammation was studied using fluorophotometry to validate the use of animal studies as a useful model. Bovine ciliary epithelium was cultured and found to express class II only in the presence of gamma interferon. Rat ciliary epithelium can function as an antigen presenting cell.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00230-04 LI

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)
Modulation of Retinal Vascular Permeability by Inflammatory Mediators

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
Others:	Rebecca Gurley	M.S.	Biologist	LI, NEI
	Benjamin Rubin	M.D.	Senior Staff Fellow	LI, NEI
	Horst Helbig	M.D.	Special Volunteer	LI, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Clinical Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.43	0.03	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Retinal vascular leakage is an important mechanism of visual loss in ocular inflammatory disease. The presumed site of retinal vascular leakage is the retinal capillaries, which are composed of pericytes and endothelial cells. It is likely that immune- mediated disease alters pericyte or endothelial function in a manner that produces vascular leakage. This project is concerned with quantifying the specific mediators that are involved in producing these changes so that more appropriate therapy can be targeted.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00247-02 LI

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Autoimmunity to the Anterior Uvea in Patients with Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
Others:	Rebecca Gurley	M.S.	Biologist	LI, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Clinical Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.77	0.17	0.6

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Many forms of anterior uveitis are presumed to be caused by autoimmunity directed toward ocular antigens. However, there has been no confirmation that an ocular-specific antigen is involved in this process. It is important to develop an understanding of the mechanisms of inflammation in patients that have anterior uveitis. The presumed site of inflammation in these patients is the iris and ciliary body. Therefore, we began to look for iris- specific proteins to which patients might have an autoimmune response. Patients with anterior uveitis were screened for autoantibodies directed against bovine iris. Antibodies were detected to a protein with a molecular weight of approximately 22,000 in some patients. When compared to a control group, patients, in general, have higher levels of this antibody than do control individuals. Until the protein is isolated and T-cell responses can be measured, the true significance of these antibodies will be unclear. Antibodies to retinal antigens are much less revealing than the corresponding T-cell responses in distinguishing patients from controls. The protein that has been identified appears to be specific to the iris and is not found in other tissues of the body. Purification of this protein for other immunologic studies is in progress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00069-12 LI

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)

Immune Responses to Ocular Antigens

PRINCIPAL INVESTIGATOR (*List other professional personnel below the Principal Investigator.*) (*Name, title, laboratory, and institute affiliation.*)

PI: Igal Gery Ph.D. Head, Section on Experimental Immunology LI, NEI

Others: See next page

COOPERATING UNITS (*if any*)

Laboratory of Molecular Biology, Division of Cancer Biology and Diagnosis, National Cancer Institute, NIH (Hanah Margalit, Ph.D.); Metabolism Branch, Division of Cancer Biology and Diagnosis, National Cancer Institute, NIH (Jay A. Berzofsky, M.D.)

LAB/BRANCH

Laboratory of Immunology

SECTION

Section on Experimental Immunology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
8.03	7.63	0.4

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (*Use standard unreduced type. Do not exceed the space provided.*)

This project is aimed at learning about the pathogenesis of inflammatory eye diseases which are grouped under the term "uveitis." Our effort in FY 1989 focused on studies in both experimental animals and humans.

The study with animals has extended our knowledge concerning the peptide determinants of the retinal interphotoreceptor retinoid-binding protein (IRBP), which are capable of inducing an ocular disease, experimental autoimmune uveoretinitis (EAU), in animals. EAU is considered a model for certain uveitic conditions in man. The studies revealed that the active site of the highly uveitogenic peptide determinant "R14" (sequence 1169-1191 of IRBP) was found to localize in the 10-amino acid sequence 1182-1191. Two more uveitogenic peptide determinants were identified in the IRBP molecule. IRBP exhibits a 4-fold repeat structure, and the two additional peptides are "repeats" of peptide R14. More data have been accumulated to establish the close association between the "immunodominance" of peptide determinants and their capacity to induce EAU and immune responses. Testing the uveitogenic and immunogenic capacities of IRBP and its peptides in various inbred strains of rats and mice have revealed that the immunological activities of the peptides depend on the genetic makeup of the tested animal.

In the study with human material, uveitis patients were examined for their immune responses toward two retina-specific proteins, IRBP and S-antigen, as well as toward four peptides of these proteins that were found to be uveitogenic in experimental animals. Cellular immune responses to the retinal antigens and their peptides were detected in a large portion of the patients. Furthermore, some of these patients exhibited substantially high levels of resonse to both proteins and to all tested peptides.

Principal Investigator (Continued)

Others:	Marc de Smet	M.D.	Visiting Associate	LI, NEI
	Satoshi Kotake	M.D.	Visiting Fellow	LI, NEI
	Li-Hong Hu	M.D.	Visiting Fellow	LI, NEI
	Charles Egwuagu	Ph.D.	Staff Fellow	LI, NEI
	Barbara Vistica	B.A.	Microbiologist	LI, NEI
	Shigeto Hirose	M.D.	Visiting Fellow	LI, NEI
	Chi-Chao Chan	M.D.	Medical Officer	LI, NEI
	Hiroki Sanui	M.D.	Visiting Fellow	LI, NEI
	Takao Tanaka	M.D.	Visiting Fellow	LI, NEI
	Mihoko Kusuda	M.D.	Visiting Fellow	LI, NEI
	Satoshi Kotake	M.D.	Visiting Fellow	LI, NEI
	Robert B. Nussenblatt	M.D.	Clinical Director	LI, NEI

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00232-04 LI

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Interferon System in Cellular Function and Disease

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	John J. Hooks	Ph.D.	Head, Section on Immunology and Virology	LI, NEI
Others:	Barbara Detrick	Ph.D.	Expert	LI, NEI
	Caroline Percopo	B.S.	Biologist	LI, NEI
	Christian Hamel	M.D.	Visiting Fellow	LI, NEI

COOPERATING UNITS *(if any)*

New York University, School of Medicine (Jan Vilcek, M.D.); Head, Tumor Biology Section, Laboratory of Biology, Division of Cancer Etiology, National Cancer Institute (Charles Evans, M.D.)

LAB/BRANCH

Laboratory of Immunology

SECTION

Section on Immunology and Virology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.1	0.7	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The interferon (IFN) protein can modify a variety of biological activities and is considered one of the body's regulatory proteins. Numerous studies have indicated that the IFNs are potent immunoregulators. During the past year, we have been studying the ways in which IFN proteins interact with cells of the immune system and how this interaction may modify immune reactivity.

Using immunocytochemical analysis, we have developed a sensitive method of identifying the lymphokines IFN-γ and interleukin 2 (IL-2) at the site of tissue damage. We have identified these lymphokines in inflammatory eye diseases. The presence of these lymphokines is associated with a lymphocyte infiltrate predominantly of T-cell origin and with the expression of major histocompatibility complex (MHC) class II antigens on both the infiltrating cells and the retinal pigment epithelial (RPE) cells.

Experimentally we have shown that this direct intravitreal inoculation of recombinant rat IFN-γ results in the expression of MHC Class II antigen (Ia) in a variety of ocular cells. In conjunction with Ia expression, two striking changes were noted: an iritis and infiltrating cells in the inner retinal layers. Both of these phenomena have been observed in certain inflammatory eye diseases.

These observations indicate that IFN-γ-induced MHC class II antigen expression may serve as a local amplification system in autoimmune and inflammatory eye disease. A better understanding of the role of lymphokines in the mechanisms involved in the development of autoimmunity and inflammation may be beneficial in developing treatments for these diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00233-04 LI

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)

Studies on the Bioregulatory Aspects of the Retinal Pigment Epithelial Cell

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	John J. Hooks	Ph.D.	Head, Section on Immunology and Virology	LI, NEI
Others:	Barbara Detrick	Ph.D.	Expert	LI, NEI
	Caroline Percopo	B.S.	Biologist	LI, NEI
	Laura Caspers-Velu	M.D.	Visiting Associate	LMOD, NEI
	Shuji Suzuki	M.D.	Visiting Associate	LI, NEI

COOPERATING UNITS *(if any)*

Hôpital St. Louis, France (Lawrence Boumsell, M.D.); Institute Gustave Rousse, France (Alain Bernard, M.D.); National Institute of Dental Research, NIH (Reuben Siraganian, M.D.)

LAB/BRANCH

Laboratory of Immunology

SECTION

Section on Immunology and Virology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.96	1.76	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The retinal pigment epithelial (RPE) cell is a major regulatory cell in the eye. That is, the RPE cell exerts a variety of actions in maintaining retinal integrity and function. In order to study this cell more effectively in vivo and in vitro, we have produced monoclonal antibodies directed against human RPE cells.

Using immunoperoxidase assays (ABC), we have identified two mouse IgG monoclonal antibodies that react with the human RPE cell. The monoclonal antibodies are both specific for the RPE cell within the eye because they do not react with any other ocular structures. Moreover, these antibodies do not cross-react with human skin, kidney, or peripheral mononuclear cells. These antibodies recognize cell surface molecules, which are highly conserved since they can be found in man, monkey, rat, mouse, cow, chicken, and frog.

Since these antibodies detect epitopes present solely on RPE cells, they provide us with the unique opportunity to evaluate a variety of aspects of RPE cell development and function. Studies on RPE cell development indicate that the epitopes appear only after the cells have begun terminal differentiation. Studies on RPE migration also demonstrate the value of these antibodies in evaluating epiretinal membrane formation.

These are the first monoclonal antibodies directed solely at the human RPE cell. Further characterization and studies with this antibody should prove useful in the identification of RPE cells in situ and in vitro. Moreover, this immunoglobulin will allow us to probe the bioregulatory functions of the cell.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00234-04 LI

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)
MHC Class II Antigens in the Pathogenesis of Inflammatory Diseases

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	John J. Hooks	Ph.D.	Head, Section on Immunology and Virology	LI, NEI
Others:	Barbara Detrick	Ph.D.	Expert	LI, NEI
	Caroline Percopo	B.S.	Biologist	LI, NEI
	Chi-Chao Chan	M.D.	Medical Officer	LI, NEI
	Robert B. Nussenblatt	M.D.	Clinical Director	NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Immunology and Virology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.4	0.3	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

MHC class II antigens, HLA-DR in the human and Ia in the mouse, are membrane-bound glycoproteins that are encoded by genes of the major histocompatibility complex. Expression of these antigens is of great functional importance for the initiation and perpetuation of immune responses. In a number of immunopathologic conditions, HLA-DR antigen negative cells are stimulated to express class II antigens. In these cases, an immunologic role has been postulated for the class II antigen expression.

During the past year, we determined whether class II antigens are expressed in certain diseases, as well as evaluated their possible role in autoimmune and inflammatory diseases. Initial studies identified cells in the anterior segment and cells in the retina (RPE cell) that express class II antigens during inflammatory eye diseases. Treatment with monoclonal anti-Ia antibodies diminished the clinical disease and the expression of MHC class II antigens.

The role of the MHC class II molecules in immune reactivity is to enable cells to present antigens to sensitized T-lymphocytes. We have preliminary evidence that the rat rpe cell that expresses Ia antigen is capable of presenting antigen to T-cells.

These studies on MHC class II antigen expression in localized autoimmune diseases provide evidence that the activation of these antigens may contribute to the immunopathogenesis of these diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00240-03 LI

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Virus Infections in the Eye

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	John J. Hooks	Ph.D.	Head, Section on Immunology and Virology	LI, NEI
Others:	Susan Robbins	Ph.D.	Postdoctoral Fellow	LI, NEI
	Christian Hamel	M.D.	Visiting Fellow	LI, NEI
	Barbara Detrick	Ph.D.	Expert	LI, NEI
	Caroline Percopo	B.S.	Biologist	LI, NEI

COOPERATING UNITS *(if any)*

See next page

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SECTION

Section on Immunology and Virology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.9	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

During the past year, we have initiated studies to evaluate the various virologic and immunopathologic processes which occur when viruses replicate in the ocular microenvironment. This is a new project comprising three areas: (1) evaluation of virus spread in HSV-1-induced retinitis. (2) studies on coronavirus infection in ocular and optic nerve cells; and (3) determination of the possible roles of other viruses in human eye diseases.

Retinitis following anterior chamber inoculation of herpes simplex virus (HSV-1) is an interesting model of viral spread and virus-induced disease. In the past year, we elucidated some of the pathologic mechanisms involved in this disease. We found that footprints of the immune system (IFN-γ and MHC class II antigen expression) can be identified in the protected retina, strongly indicating that it is the immune system that protects the retina from destruction by virus.

Numerous human degenerative and inflammatory diseases of the retina are of unknown origin. We have developed a virus-induced murine disease that may be considered a model for degenerative diseases of the retinal pigment epithelium (RPE) and photoreceptors in man. Intravitreal inoculation of murine coronavirus (JHM) results in replication of a virus in the retina that is associated with a severe, long-term pathology in the retina, but not in the anterior segment of the eye. Viral replication was detected in the RPE cells, photoreceptors, and Müller-like cells of the neural retina.

Cooperating Units

Wilmer Eye Institute, The Johns Hopkins Hospital, Baltimore, MD (Judith Whittum-Hudson, Ph.D.); Department of Pathology, Uniformed Services University for Health Sciences, Bethesda, MD (Katherine Holmes, Ph.D.); Department of Ophthalmology, Ruprecht-Karl's University, Heidelberg, Germany (Ellen Kraus-Mackiw, M.D.); Department of Ophthalmology, University of Munich, Munich, Germany (Otto F. Scheiffanth (M.D.)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00184-07 LI

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cellular Mechanisms in Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Rachel R. Caspi	Ph.D.	Visiting Associate	LI, NEI
Others:	Francois Roberge	M.D.	Visiting Associate	LI, NEI
	Chi-Chao Chan	M.D.	Medical Officer	LI, NEI
	William Leake	M.S.	Biologist	LI, NEI
	Makoto Higuchi	M.D.	Visiting Fellow	LI, NEI
	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI

COOPERATING UNITS *(if any)*

Immunology Research Unit, Klinikum Stegliz, Freie Universitat Berlin, Federal Republic of Germany

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Laboratory of Immunology

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Section on Immunoregulation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.86	1.82	0.04

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Cellular mechanisms of ocular immunologically mediated disease are being studied in animal models of experimental autoimmune uveoretinitis, (EAU). In vivo functional long-term T-cell lines and T-cell clones are developed and maintained in vitro from lymphoid organs of experimental animals immunized with uveitogenic ocular proteins. The phenotype and functional properties of these cells, as well as their interaction with ocular resident cells are being studied. The goal of these studies is to identify the immunoreactive cells and mediators as well as the pathogenic mechanisms involved in the intraocular inflammatory process.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00258-01 LI

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Experimental Autoimmune Uveitis in the Mouse

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Rachel R. Caspi	Ph.D.	Visiting Associate	LI, NEI
Others:	Francois Roberge	M.D.	Visiting Associate	LI, NEI
	Chi-Chao Chan	M.D.	Medical Officer	LI, NEI
	William Leake	M.S.	Biologist	LI, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Immunoregulation

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.52	0.32	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A new model of experimental autoimmune uveitis (EAU) is being developed in the mouse species, which has until now been considered refractory to induction of ocular autoimmunity. Different retinal antigens, as well as various immunization protocols are being evaluated for efficacy of EAU induction. The pathological manifestations, disease course, and genetic background of susceptibility to disease in murine EAU are being studied in relationship to the induction protocol. The goal of these studies is to establish a rodent model of EAU in the mouse species, which offers some important advantages over other rodent models of EAU. The extensive knowledge of the immunological parameters of the mouse and the availability of genetically defined strains will be of great value in the study of cellular mechanisms and immunogenetics of ocular autoimmune disease.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00222-04 LI

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Immunopathology in the Eyes with Experimental Autoimmune Uveitis (EAU)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Chi-Chao Chan	M.D.	Medical Officer	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	Igal Gery	Ph.D.	Head, Section on Experimental Immunology	LI, NEI
	Rachel R. Caspi	Ph.D.	Visiting Associate	LI, NEI
	Francois Roberge	M.D.	Visiting Associate	LI, NEI
	Ming Ni	M.D.	Visiting Fellow	LI, NEI

COOPERATING UNITS *(if any)*

University of Tokyo, School of Medicine (Manabu Mochizuki, M.D.)

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Section on Immunoregulation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.34	1.34	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The identification and topographic localization of immunocompetent cells and alteration of surface markers on ocular resident cells in rodents with experimental autoimmune uveitis (EAU) by active immunization or adoptive transfer were analyzed by immunohistochemical studies. The lymphocyte population at the inflammatory sites was found to change markedly during the course of disease. In the early stage, T-helper/inducers were found to be the predominant cells in the eye. A relative increase of T-suppressor/cytotoxic cells was observed in the late stage. The expression of major histocompatibility complex class II antigens on such ocular resident cells as those found in retinal pigment epithilium (RPE), retinal endothelium, and ciliary epithelium, as well as keratocytes and fibroblasts, was observed in different models of EAU in rats. This antigen expression may play a certain role in the pathogenesis of EAU. Both the infiltrating cell subpopulation and the expression of class II antigens on ocular resident cells enhanced by interferon gamma can be modulated by different immunosuppressive agents.

The immunopathology of eyes of mice with EAU can be presented as a focal chronic granulomatous inflammation. Subretinal neovascularization may develop. The expression of major histocompatibility complex class II antigens is confined to those ocular resident cells located at the inflammatory sites.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00224-04 LI

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Sympathetic Ophthalmia: Immunopathological Findings

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Chi-Chao Chan	M.D.	Medical Officer	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
	Toichiro Kuwabara	M.D.	Chief, Laboratory of Ophthalmic Pathology	LI, NEI

COOPERATING UNITS *(if any)*

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Section on Immunoregulation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.12	0.12	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Immunocompetent cells and ocular resident cells in the tissues from patients with a clinical diagnosis of sympathetic ophthalmia were examined immunohistochemically. The choroidal infiltrates were shown to be composed primarily of T-lymphocytes. Different numbers of macrophages and B-lymphocytes were present in each case. A variety of immunopathological and histopathological findings may occur in clinically diagnosed sympathetic ophthalmia. The immunopathology resembles experimental autoimmune uveitis induced by retinal soluble model. Exposure of uveal tissue outside the eye and adjuvant effect may be important in the pathogenesis of this disease in humans.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00225-04 LI

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Post-Inflammatory Complications in Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Chi-Chao Chan	M.D.	Medical Officer	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	Francois Roberge	M.D.	Visiting Associate	LI, NEI

COOPERATING UNITS *(if any)*

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SECTION
Section on Immunoregulation

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.12	0.12	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Complications of post-inflammation in uveitis patients includes destruction of photoreceptors, gliosis, choroidal scar, and formations of cyclitic membrane, snowbanking, and preretinal membrane. Post-inflammatory membrane composition may play an important role in the cause of complications associated with uveitis. In this study, eyes enucleated from patients with end stages of chronic anterior uveitis (formation of cyclitic membrane), pars planitis (formation of preretinal membrane) were evaluated immunohistochemically. Glial cells and proliferating Müller cells were the major cellular components in these membranes. Basement membrane-like components and new collagens were the major extracellular membrane components.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00226-04 LI

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Immunopathology of Ocular Onchocerciasis and Other Parasitic Diseases

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Chi-Chao Chan	M.D.	Medical Officer	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI

COOPERATING UNITS *(if any)*

National Institute of Allergy and Infectious Diseases, Clinical Parasitic Diseases Section (Eric A. Ottesen, M.D.); World Health Organization (K. Awadzi, M.D.)

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Laboratory of Immunology

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Section on Immunoregulation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.33	0.33	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Ocular specimens and sera from 12 patients with onchocerciasis and 10 controls were studied. A mild to moderate chronic inflammatory cellular infiltration was present in the conjunctiva of the onchocerciasis patients. T-lymphocytes were the predominant inflammatory cells, with the T-suppressor subset being significantly increased in the onchocerciasis patients, compared to controls. In the onchocerciasis patients, such nonlymphoid cells in the conjunctiva and iris as vascular endothelia, pericytes, and fibroblasts showed an increase in expression of class II antigens. The anti-*Onchocerca volvulus* antibodies in the sera and aqueous humor were significantly higher in the patients compared to the controls. These findings suggest that T-cells are important in the ocular immune response to *Onchocerca* and that expression of class II antigens on nonlymphoid cells and the humoral factors may play a critical role in the ocular onchocerciasis.

Retinal autoantibodies found in sera of these 12 patients were bound to the inner retinal layer and photoreceptors. Such autoimmune antibodies may play a role in the pathogenesis of the retinal degeneration and optic atrophy that occurs as a consequence of onchocerciasis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00241-03 LI

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Immunopathology of Ocular Diseases in Humans

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Chi-Chao Chan	M.D.	Medical Officer	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
	Ming Ni	M.D.	Visiting Fellow	LI, NEI
	Toichiro Kuwabara	M.D.	Chief, Laboratory of Ophthalmic Pathology	LI, NEI

COOPERATING UNITS *(if any)*

University of Minnesota, Department of Ophthalmology (Edward J. Holland, M.D.); Mayo Clinic, Department of Ophthalmology, Rochester, MN (David C. Herman, M.D.)

LAB/BRANCH

Laboratory of Immunology

SECTION

Section on Immunoregulation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.27	0.27	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Specimens from human ocular tissues with various diseases, such as uveitis, conjunctival and corneal diseases, and ocular metabolic genetic diseases and tumors, were studied using the immunoperoxidase technique and light and electron microscopic evaluation. In uveitis, immunocompetent cells and lymphokines are critical in the reflection of clinical diagnosis, disease course, and prognosis. In non-uveitis diseases, alteration of cellular membrane surface markers and intracytoskeleton on the ocular resident cells may imply damages and abnormalities in these diseases. The relationship between infiltrating inflammatory cells and other cells may play some significant roles in the clinical behavior of various diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00249-02 LI

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cytokines in Human Intraocular Fuids

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Janet L. Davis	M.D.	Senior Staff Fellow	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI

COOPERATING UNITS *(if any)*

Eye Research Institute, Boston, MA (Alex E. Jalkh, M.D.); Eye Research Institute, Boston, MA (Charles Schepens, M.D.); University of Miami, Miami, FL (Harry W. Flynn, Jr., M.D.)

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Section on Immunoregulation

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NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.32	0.32	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The relationship of intraocular cytokines to human retinal detachment and proliferative vitreoretinopathy (PVR) was explored in 1988 by directly assaying human specimens for the presence of interleukin 1 (IL-1) and interleukin 2 (IL-2). In 1989, we expanded the project to include a rabbit model of PVR. The intraocular fluids of 18 rabbits in three treatment groups were assayed for the presence of IL-1, IL-2, and transforming growth factor β (TGF-β) at various times during the course of PVR. No definite pattern of IL-1 activity was detected; however, both TGF-β and IL-2 activity appeared to follow a time course related to stage of disease. Increased IL-2 activity was noted in eyes with PVR beginning 3 weeks after induction of the disease. Increased levels of active TGF-β were noted at about the same time in PVR eyes. These preliminary findings support a physiological role of TGF-β in PVR and also suggest that a different cytokine with IL-2 activity is involved in the cellular proliferative processes of PVR.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00231-04 LI

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cell Surface Antigens on Retinoblastoma Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Barbara Detrick	Ph.D.	Expert	LI, NEI
Others:	John J. Hooks	Ph.D.	Head, Section on Immunology and Virology	LI, NEI
	Gerald J. Chader	Ph.D.	Director of Intramural Research	NEI
	Caroline Percopo	B.S.	Biologist	LI, NEI

COOPERATING UNITS *(if any)*
Head, Tumor Biology Section, Laboratory of Biology, National Cancer Institute (Charles Evans, M.D.); Walter Reed Army Medical Center (Norman Katz, M.D.); University of Maryland, Baltimore (Meryln Rodrigues, M.D.)

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SECTION
Section on Immunoregulation

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.6	0.4	0.2

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Retinoblastoma (RB), an ocular tumor of childhood, consists of multipotent embryonic cells that have the potential to differentiate into neuronal or glial-like components. MHC class II antigens (HLA-DR, DQ, DP) are integral glycoproteins that are critical in immune regulation. The identification of these determinants on a variety of primitive stem cell types and tumor cells arrested at selected phases of their cell cycle has suggested that these molecules play a role in cellular differentiation.

Recently, we demonstrated the presence of the class II molecules on RB cells. In addition, the modulation of HLA-DR by IFN-γ as well as the preferential expression of this determinant over HLA-DQ is described. Double-labeling experiments revealed that HLA-DR antigen is shared concomitantly with cells of glial and neuronal character.

Based on these initial studies, additional investigations are in progress. One approach focuses on the correlation of class II antigen expression with cellular differentiation. A second examines the prognostic significance of these molecules on retinoblastoma cells and the possible relationship these proteins may have to the modulation and management of this tumor. Finally, a third study will examine the role of IFN-γ as a differentiating agent of this tumor.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00235-04 LI

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Identification and Modulation of Class II Antigens

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Barbara Detrick	Ph.D.	Expert	LI, NEI
Others:	John J. Hooks	Ph.D.	Head, Section on Immunology and Virology	LI, NEI
	Chi-Chao Chan	M.D.	Medical Officer	LI, NEI
	Caroline Percopo	B.S.	Biologist	LI, NEI
	Robert B. Nussenblatt	M.D.	Clinical Director	NEI

COOPERATING UNITS *(if any)*
University of Pennsylvania (G. Aguirre, D.D.S., Ph.D.); Duke University (Barton F. Haynes, M.D.); Paris, France (Laurence Boumsell, M.D.).

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Immunoregulation

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.44	0.34	0.1

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Class II antigens are integral glycoproteins encoded by genes in the major histocompatibility complex. Their expression is critical to immune reactivity. Although most immune cells constitutively express class II antigens, some nonimmune cell types can be induced to demonstrate these molecules under selected conditions, such as an immunologic or degenerative event. Based on our earlier data, demonstrating that retinitis pigmentosa patients had an alteration in IFN-γ production and class II antigen expression, we expanded our studies to evaluate class II antigen expression in a variety of ocular situations. We found that the retinal pigment epithelium (RPE) cell did not express class II antigen in the normal eye. In contrast, the RPE cell did express these molecules in a retinal degenerative disorder (retinitis pigmentosa) and in two ocular inflammatory diseases (sympathetic ophthalmia and uveitis). Using the experimental autoimmune uveitis (EAU) animal model of ocular autoimmune disease, we demonstrated that the RPE cell is activated to express class II antigens prior to clinical and histopathological evidence of the disease. Finally, we demonstrated that EAU could be altered with anti-Ia therapy. In this study, EAU animals receiving monoclonal anti-Ia antibodies experience not only less ocular inflammation but also a delay in the onset of EAU. Moreover, immunocytochemistry analysis revealed that eyes from these animals expressed less Ia antigen as well as a diminution of infiltrating macrophages and lymphocytes. These data show that anti-Ia treatment significantly modifies the course of EAU in the rat. We have also demonstrated that direct inoculation of recombinant IFN-γ results in the expression of MHC class II (Ia) in a variety of ocular cells. We are continuing to investigate the effects of other potent modulators with the hope that an alteration in activation or expression of these molecules may modify the disease process to the benefit of the host.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00248-02 LI

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Magainin Therapy of Infectious Keratitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Phuc Le Hoang	M.D.	Visiting Scientist	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	Janet L. Davis	M.D.	Senior Staff Fellow	LI, NEI
	Rashid Mahdi		Biologist	LI, NEI

COOPERATING UNITS *(if any)*
Human Genetics, National Institute of Child Health and Human Development (Michael Zasloff, M.D., Ph.D.); Human Genetics, National Institute of Child Health and Human Development (Charles Bevins, M.D., Ph.D.)

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Immunoregulation

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.0	0.5

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies are being conducted in animals to determine the in vivo activity of a new class of antimicrobial peptides isolated from the skin of the African frog *Xenopus laevis* and called magainins. This family of peptides consists of two closely related peptides, each 23 amino acids, that inhibit growth of numerous species of bacteria and fungi in vitro. An animal model of experimental bacterial keratitis induced in adult New Zealand white rabbits was used to determine the in vivo relevance of the antimicrobial activity of magainins. *Pseudomonas aeruginosa* corneal infection was primarily considered because it is the most destructive and the most difficult to treat corneal infection in humans. Each cornea was infected by an intrastromal injection of 100 bacteria. Topical treatment with magainin drops or ocular ointment was started either 4 hours or 20 hours after the infection. The control animals were either not treated or treated with the vehicle (PBS or petrolatum plus mineral oil). These preliminary studies demonstrated the in vivo activity of the magainin by showing a less severe corneal abscess in the treated animals with a delayed onset of the abscess as compared to the control animals. Although the animals could tolerate the treatment well, magainin drops and ointment induced a chemosis with a conjunctival hyperhemia by themselves which can aggravate the conjunctival inflammation related to the infection.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00075-11 LI

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Immune Functions in Ocular Diseases of Obscure Etiology

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
Others:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
	William Leake	M.S.	Biologist	LI, NEI
	Rashid Mahdi		Biologist	LI, NEI
	Janet L. Davis	M.D.	Senior Staff Fellow	LI, NEI
	Marc de Smet	M.D.	Senior Staff Fellow	LI, NEI
	Benjamin Rubin	M.D.	Senior Staff Fellow	LI, NEI
	Igal Gery	M.D.	Head, Section on Experimental Immunology	LI, NEI

COOPERATING UNITS *(if any)*

University of Tokyo, Tokyo, Japan (Manabu Mochizuki, M.D.)

LAB/BRANCH

Laboratory of Immunology

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Section on Immunoregulation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.42	0.42	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In vitro tests of cellular immune functions and lymphocyte subsets are being performed in a masked study of patients with ocular toxoplasmosis, pars planitis, Behcet's disease, geographic choroiditis, and chorioretinitis of unknown origin. Crude ocular antigens, purified uveitogenic soluble antigen (S-antigen), interphotoreceptor retinoid-binding protein (IRBP) of the retina, and uveitogenic fractions of the retinal S-antigen are being used in a lymphocyte microculture technique to evaluate the presence of cellular immune memory to ocular tissues. In addition, purified antigens from the toxoplasmosis organism are also being tested in this in vitro system. A subgroup of patients with posterior uveitis has been identified as having this immunologic memory. The definition of lymphocyte subsets in the blood and eyes in these patients by monoclonal antibodies may shed light on the basic mechanisms of uveitis and may be used as a guide for specific immunologic therapy. Sera from these patients are also being evaluated. Using the technique of chorioretinal biopsy, a new retinopathy in AIDS appears to have been identified.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00092-11 LI

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)
HLA, ABO, and B-cell Alloantigens and Ocular Inflammatory Disease

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
Others:	Charles Egwuagu	Ph.D.	Staff Fellow	LI, NEI

COOPERATING UNITS *(if any)*
L'Hôpital de la Pitié, Paris, France (Phuc Le Hoang, M.D.)

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Immunoregulation

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.03	0.03	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Patients with ocular toxoplasmosis, pars planitis, Behcet's disease, and chorioretinitis of unknown origin are being studied to determine the phenotype frequency of the HLA, ABO, and B-cell alloantigens. Because the B-cell alloantigens or DR antigens are thought to play a role in the immunologic response to antigens, these findings will complement other immune uveitis studies being conducted simultaneously. Restriction fragment analysis has begun to complement these HLA studies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00094-11 LI

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Immune Mechanisms in Experimental Autoimmune Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
Others:	Yujiro Fujino	M.D.	Visiting Associate	LI, NEI
	Stephan Thurau	M.D.	Special Volunteer	LI, NEI
	Rashid Mahdi		Biologist	LI, NEI
	Evelyn Beraud	M.D.	Visiting Associate	LI, NEI
	Benjamin Rubin	M.D.	Senior Staff Fellow	LI, NEI
	Phuc Le Hoang	M.D.	Visiting Scientist	LI, NEI

COOPERATING UNITS *(if any)*

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Section on Immunoregulation

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.35	1.25	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Lewis rats and nonhuman primates, immunized at a site distant to the eye with the retinal soluble antigen (S-antigen) in complete Freund's adjuvant, develop experimental autoimmune uveitis (EAU). Lymph node cells and peripheral lymphocytes from immunized animals manifested significant cellular immune responses measured by the lymphocyte culturing technique. The cyclosporines, a family of drugs with specific anti-T-cell activity, have been found to be exceptionally effective in protecting rats with EAU. Attempts at local immunosuppressive therapy in order to prevent EAU have begun. Newer cyclosporines, particularly D and G, have been evaluated in this model, with their efficacy compared to that of CsA. The use of "natural" immunomodulatory modes such as T-cell vaccination are being developed. The effects of FK506, an agent that is 10 to 30 times as effective as cyclosporine, have also been investigated, as have autoagonists to platelet-activating factors.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00115-11 LI

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cyclosporine Therapy in Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
Others:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
	Janet L. Davis	M.D.	Senior Staff Fellow	LI, NEI
	Chi-Chao Chan	M.D.	Medical Officer	LI, NEI
	Marc de Smet	M.D.	Senior Staff Fellow	LI, NEI
	William Leake	M.S.	Biologist	LI, NEI

COOPERATING UNITS *(if any)*

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Section on Immunoregulation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.55	0.54	0.01

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Cyclosporine, an endecapeptide fungal product with specific anti-T-cell characteristics, will be administered to patients with sight-threatening ocular inflammatory disease of noninfectious origin who have failed on either corticosteroid or cytotoxic agent therapy. This will be done to test cyclosporine's efficacy in the treatment of uveitis. Within the context of these ongoing studies, the effect of hydergine in reversing cyclosporine-induced nephrotoxicity is being evaluated in a randomized, masked, crossover study. In addition, selected patients whose uveitis has been well controlled on cyclosporine for 1 year or more are undergoing kidney biopsies to evaluate the long-term effects of this agent. A phase I/II randomized trial using cyclosporine A and cyclosporine G has begun.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00228-04 LI

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Study of Ocular Glial Cell Involvement in Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Francois Roberge	M.D.	Visiting Associate	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	Rachel Caspi	Ph.D.	Visiting Associate	LI, NEI

COOPERATING UNITS *(if any)*

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Laboratory of Immunology

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Section on Immunoregulation

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.82	0.82	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This work extended our ongoing study of interactions between the retinal glial Müller cell and T-lymphocytes. In an in vitro coculture system, Müller cells had been shown to exert a profound inhibitory influence on the proliferation of T-helper cell lines through a membrane-bound factor. Investigations of the nature of the inhibitory moiety revealed that it was sensitive to proteinase. Further studies showed that the expression of the factor on the surface of Müller cells could be suppressed by glucocorticoids.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00245-02 LMOD

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Molecular Biology of Cataracts

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Teresa Borras	Ph.D.	Biologist	LMOD, NEI
Others:	Anna Rodokanaki	M.D.	Visiting Fellow	LMOD, NEI
	Ignacio Rodriguez	Ph.D.	Staff Fellow	LMOD, NEI
	Pedro Gonzalez	Ph.D.	Special Volunteer	LMOD, NEI

COOPERATING UNITS *(if any)*

Department of Chemistry, Karolinska Institute, Stockholm, Sweden (Dr. Hans Jörnvall, Ph. D.); Diabetes Programs Branch, National Institute of Diabetes and Digestive and Kidney Diseases, NIH (Flora de Pablo, M.D.)

LAB/BRANCH

Laboratory of Mechanisms of Ocular Diseases

SECTION

Section on Cataracts

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	2.8	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Investigation of the molecular mechanisms of hereditary cataracts continues, using as a model the nuclear hereditary cataract of strain 13/N guinea pigs. This year, we focused on the further characterization of the cDNA and expression of the gene encoding the ζ-crystallin protein. ζ-crystallin, a major constituent of the guinea pig lens, appears to be altered in the eyes of the cataractous animals.

We isolated a new cDNA clone that added 361 nucleotides to the 3' region of the mRNA and contains the polyA$^+$ adenylation signal. The full-length mRNA contains 1,842 nucleotides. Developmental expression studies in the lens showed that the ζ gene is expressed in a 50-day-old embryo and keeps a constant mRNA level through the animal's first year of life.

ζ-crystallin mRNA was also detected in smaller concentrations in the liver and in trace amounts in the kidney and brain. In the liver, two mRNA species were present, suggesting perhaps a different processing mechanism than that of the lens. Hybridization experiments using the ζ-cDNA probe on the lens RNA of the cataractous animals showed that a distinct lower-molecular-weight mRNA was present in the lens of the homozygous animal. The heterozygous animal conserved both the normal and the mutated species. These results confirmed that the ζ gene is definitely involved in the formation of the guinea pig cataract.

Previously we reported the existence of a similarity between ζ-crystallin and the enzyme alcohol dehydrogenase, indicating recruitment of the enzyme to become a lens protein. This past year, we extended the comparison to 20 members of the alcohol/polyol dehydrogenase family, showing that the conserved or altered characteristics in ζ-crystallin are remarkably coupled with an increase in protein stability, a stability very much needed for its new function as a structural protein of the lens.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00201-05 LMOD

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Molecular Biology of Aldose Reductase

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Deborah Carper	Ph.D.	Biologist	LMOD, NEI
Others:	Caroline Graham	B.A.	Chemist	LMOD, NEI
	Masayuki Kaneko	M.D.	Visiting Associate	LMOD, NEI
	Susan Old	Ph.D.	Staff Fellow	LMOD, NEI

COOPERATING UNITS *(if any)*
Chihiro Nishimura, National Children's Medical Research Center, Tokyo, Japan

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Laboratory of Mechanisms of Ocular Diseases

SECTION
Section on Cataracts

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	2.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Aldose reductase (AR) is implicated in some of the disabling complications of diabetes, including neuropathy, retinopathy, and cataracts. Our studies are aimed at further clarifying the role of AR in diabetes and facilitating the design of a new generation of AR inhibitors based on the structural aspects of the protein. To this end, we have completed description of the primary structure of AR and characterized a number of genes for AR, of which one appears to be a functional gene. We have shown that AR expression is induced when several cell types, including two target tissues of diabetes, are exposed to hypertonic conditions.

One putative functional gene for rat AR and three processed pseudogenes have been characterized. The functional gene currently comprises 9 exons. The 3' end is identical to the mRNA. Further cloning is now in progress to complete the 5' end.

AR protein and mRNA increase between 10-fold and 60-fold when dog lens, rat kidney cortex, or Chinese hamster ovary cells are exposed to hypertonic conditions (300 mosM, media supplemented with sodium chloride, raffinose, sorbitol, or glucose, bringing the total osmolarity to 600 mosM). The elevation of AR mRNA can be detected after as little as 4 hours, with a peak at 24 hours.

The characterization of the AR gene and the studies on AR expression in vitro will set the foundation for studies on the regulation of gene expression in diabetes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00189-06 LMOD

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Oxidation of Proteins in Cataractogenesis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI: Donita L. Garland Ph.D. Research Chemist LMOD, NEI

COOPERATING UNITS *(if any)*

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Laboratory of Mechanisms of Ocular Diseases

SECTION
Section on Cataracts

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Oxidative changes of lens proteins are thought to occur with aging and to contribute to the development of cataracts. The goals of this project are to determine (1) the extent of oxidative modification of crystallins and metabolic enzymes in both normal and cataractous lenses, (2) the nature of the modifications and mechanisms leading to the changes, and (3) the effect of the modifications on structure and function of lens proteins. Bovine and rat lenses are used. The approach is to study the modifications of lens proteins after treatment in vitro by metal-catalyzed oxidation systems.

Structural alterations induced by these oxidative systems were examined by circular dichroism and peptide mapping. Trace metal analysis of bovine aqueous and rat and bovine lenses indicated that copper and iron are both present in micromolar concentrations. Low-molecular-weight rat lens proteins that comigrate with γ-crystallins and have ionic properties similar to those of γ-crystallins interact with copper. These results support the possibility that metal catalyzed oxidative reactions may contribute to age-related changes in lens and the trabecular meshwork.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00237-04 LMOD

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Characterization of the Lens

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Paul Russell	Ph.D.	Research Chemist	LMOD, NEI
Others:	Takahiko Yamada	M.D.	Visiting Associate	LMOD, NEI

COOPERATING UNITS *(if any)*

Howe Laboratory and Harvard University (D.L. Epstein)

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Laboratory of Mechanisms of Ocular Diseases

SECTION

Section on Cataracts

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

With the advent of transgenic animals, it has been possible to study the influence and regulation of various genes on the development of an organism. However, this technique has not generally been used to develop cell lines for use in tissue culture. Tissue culture of the lens epithelium has been a goal of lens researchers because it may afford an opportunity to develop in vitro systems to test the efficacy of anti-cataract agents, as well as to study some mechanisms of cataract formation.

Recently obtained is a transgenic animal that has the T-antigen from the SV-40 virus linked to the α A-crystallin promoter. Cells from the lens of this animal that proliferate in the tissue culture environment have been shown to produce all the α-crystallins. In addition, the α-crystallins from these cells are found in large molecular weight aggregates and appear to undergo post-translational modification in the cells. These cells also synthesize the enzyme aldose reductase. Modification of the osmolarity of the tissue culture medium regulates the expression of this enzyme in vitro. This cell line is now one of the first cell lines with which basic questions about the molecular and cell biology of the lens epithelium can be addressed.

Along with work on the mouse lens cell line, this laboratory has studied other model systems to look at additional disease states of the eye. The calf trabecular meshwork has been examined to define the proteins present in that tissue. Comparison of those proteins to those present in the human trabecular meshwork will aid determination of how they might be influenced by various oxidative stresses in the eye.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00252-01 LMOD

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cataract in the Philly Mouse Strain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Paul Russell	Ph.D.	Research Chemist	LMOD, NEI
Others:	Masao Nakamura	M.D.	Visiting Associate	LMOD, NEI
	Deborah A. Carper	Ph.D.	Research Biologist	LMOD, NEI
	George Inana	M.D.	Medical Officer	LMOD, NEI

COOPERATING UNITS *(if any)*

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Section on Cataracts

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.8	0.8	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Philly mouse, derived from the Swiss-Webster strain, develops a cataract about 6 weeks after birth. Initial results have shown that in the lenses of these animals the epithelial cells fail to undergo complete differentiation. Biochemically, a 27 kD protein appeared to be missing in the Philly lens. This protein was found in the elongating cells at the equatorial region of the normal lens. Work showed that the 27 kD protein is the β2-crystallin and that this protein in the normal lens is a heat-stable protein. Investigation of the Philly mouse revealed that mRNA with approximately the same size as the normalβ2 mRNA is present in the Philly lens. Furthermore, it was shown that a protein present in the Philly lens is immunologically related to the β2 protein in the normal lens. This protein shares the same amino terminal as the normal β2 but lacks part of the carboxyl half of the protein. The altered protein is slightly smaller and has a more acidic isoelectric point than the normal lens β2-crystallin. Work is now in progress to sequence both the normal and the Philly β2-crystallin proteins.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00105-10 LMOD

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Structure and Composition of Lens Crystallins with Respect to Cataractogenesis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	J. Samuel Zigler, Jr.	Ph.D.	Research Biologist	LMOD, NEI
Others:	Xinyu Du	M.D.	Visiting Fellow	LMOD, NEI
	D. Balasubramanian	Ph.D.	Visiting Scientist	LMOD, NEI
	Guo-Tong Xu	M.D.	Special Volunteer	LMOD, NEI
	Vasantha Rao	Ph.D.	Visiting Fellow	LMOD, NEI

COOPERATING UNITS *(if any)*

Department of Ophthalmology, University of Tennessee (H.M. Jernigan, Jr.); Oakland University, Rochester, MI (V.N. Reddy); Alcon Laboratories (M. Lou); National Cancer Institute, (M. Krishna and P. Riesz).

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Laboratory of Mechanisms of Ocular Diseases

SECTION

Section on Cataracts

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.8	3.8	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Lens crystallins are structural proteins that comprise over 90% of the dry mass of the lens. In cataracts, the crystallins are found to be heavily modified, particularly via oxidation. It is thought that this oxidative damage is a critical factor in the etiology of lens opacification. This laboratory is working toward elucidation of the actual functions of crystallins in the normal lens. It is also determining how normal lens function is affected by modification of crystallin structure (e.g., by oxidative stress) or by change in the composition of crystallins through the loss by mutation of a particular crystallin.

One source of oxidative stress in the lens may be photooxidative processes involving endogenous sensitizing molecules. Dr. Balasubramanian has adopted a system to determine specifically the effects on crystallins of singlet oxygen (type 2 process) as opposed to the free radical species produced by type 1 processes. He has determined the relative sensitivity of different crystallins to such damage and also the amino acids which are the primary targets.

Our studies on naphthalene-induced cataract, which appears to be caused by oxidative stress, are aimed toward determining its suitability as a general model for oxidation-induced cataract. The molecular basis of cataract formation is being probed, and the biochemical effects on crystallins and metabolism measured during cataract development.

Studies on congenital cataracts in strain 13/N guinea pigs have revealed that a mutation in the gene for ζ-crystallin is likely the initiating factor for cataract development. The mechanism responsible is under study, as is the effect of loss of a major protein from the lens.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00193-06 LMOD

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)

Molecular Biology of Hereditary Eye Diseases

PRINCIPAL INVESTIGATOR (*List other professional personnel below the Principal Investigator.*) (*Name, title, laboratory, and institute affiliation.*)

PI:	George Inana, M.D.,	Ph.D.	Head, Section on Molecular Pathology	LMOD, NEI
Others:	Carmelann Zintz	Ph.D.	Staff Fellow	LMOD, NEI
	Yoshihiro Hotta	M.D.	Visiting Associate	LMOD, NEI
	Carolyn Chambers	Ph.D.	IRTA Fellow	LMOD, NEI
	Tetsuo Sasabe, M.D.,	Ph.D.	Visiting Associate	LMOD, NEI

COOPERATING UNITS (*if any*)

LAB/BRANCH

Laboratory of Mechanisms of Ocular Diseases

SECTION

Section on Molecular Pathology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.0	5.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (*Use standard unreduced type. Do not exceed the space provided.*)

Ornithine Aminotransferase Deficiency in Gyrate Atrophy: Gyrate atrophy (GA), a blinding, autosomal recessive degenerative disease of the retina and choroid of the eye, is characterized by a generalized deficiency in the mitochondrial enzyme ornithine aminotransferase (OAT). Our molecular genetic investigation of this disease has resulted in (1) the cloning and characterization of a cDNA for the human OAT, (2) the mapping of the OAT gene sequences to chromosomes 10 and X, (3) the identification of the OAT gene family and characterization of the members of the family including the functional OAT gene, (4) construction of expression clones of OAT and expression of OAT in heterologous tissues, and (5) analysis of the OAT gene and its expression in GA patients. This effort has revealed a case with a partial heterozygous deletion of the OAT gene and complete absence of the OAT mRNA. By examining family members of this GA patient, we were able to demonstrate the stable autosomal recessive inheritance of the OAT gene and expression defect in the family in addition to demonstrating the codominant mode of action of the OAT gene. Analysis of a GA patient who shows a marked decrease in the level of cellular OAT protein revealed that he is expressing only one of the two alleles of the OAT gene and that the expressed OAT contains a single point mutation resulting in an amino acid change. This amino acid change appears to modify an alpha-helical region of the OAT protein. Assay of the mutant OAT protein for mitochondrial transport/processing seems to indicate that the mutant protein fails to become processed. This project was terminated on July 1, 1989.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00243-03 LMOD

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Ocular Cells Cultured Under Normal and Diabetic Conditions

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Bruce A. Pfeffer	Ph.D.	Senior Staff Fellow	LMOD, NEI
Others:	W. Gerald Robison, Jr.	Ph.D.	Chief, Section on Pathophysiology	LMOD, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Mechanisms of Ocular Diseases

SECTION
Section on Pathophysiology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	2.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Utilizing cultured human and monkey retinal pigment epithelium (RPE), we are assessing at the cellular level what may be the earliest pathological changes in diabetic complications. Cultured RPE may be useful since these cells possess aldose reductase and generate intracellular polyol when insulted with elevated concentrations of hexose sugars, especially galactose, in their media. We have determined that taurine transport into and out of cultured RPE is impaired after cells are incubated with galactose and that this effect is preventable by including aldose reductase inhibitors (ARI) in the galactose-containing medium.

The fact that taurine transport is sodium-dependent suggests a polyol-related change in sodium homeostasis in cells that accumulate polyol in our simplified in vitro model of diabetes. Using both radiolabeled guanidine, a specific probe for sodium channels, and radioactive sodium itself, we were able to demonstrate augmented sodium ion permeability in RPE cells incubated with galactose. This effect could be significantly reduced when ARI was present in galactose-containing medium. It is likely that abnormal sodium transport in galactose-treated RPE in vitro may be representative of the pathological changes resulting from aldose reductase activity in other tissues exhibiting diabetic complications.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00149-16 LMOD

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Ultrastructure and Function of the Cells and Tissues of the Eye

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	W. Gerald Robison, Jr.	Ph.D.	Head, Section on Pathophysiology	LMOD, NEI
Others:	Nora Laver	M.D.	Visiting Associate	LMOD, NEI
	Bruce A. Pfeffer	Ph.D.	Senior Staff Fellow	LMOD, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Mechanisms of Ocular Diseases

SECTION
Section on Pathophysiology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.2	5.0	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Diabetic retinopathy is mainly a vascular disease. The earliest histopathological signs include selective loss of intramural pericytes and thickening of capillary basement membranes. Previous evidence from animal models indicated that aldose reductase inhibitors could prevent these capillary wall lesions, but only recently have aldose reductase inhibitors been tested for prevention of subsequent retinal complications of diabetes such as microaneurysms. In this study, Sprague-Dawley rats were fed diets containing 50% galactose with or without an aldose reductase inhibitor (tolrestat). After 28 months of galactose feeding, the retinal capillaries in whole mounts exhibited a marked increase in periodic-acid-Schiff (PAS) staining, extensive pericyte loss, endothelial cell proliferation, acellularity, diffuse dilation, occluded lumens, microaneurysms, and complex microvascular abnormalities, including gross dilation and formation of multiple-shunt networks. The PAS hyperchromaticity of basement membrane material and pericyte loss occurred throughout the retinal vasculature, while the microaneurysms and complex lesions were limited to the capillaries of the central and paracentral retina. As with diabetic retinopathy in humans, the changes were associated with both the arterial and venous portions of the capillary plexus. Treatment with orally administered tolrestat prevented essentially all the vessel abnormalities. Thus, long-term galactose feeding of rats induced microvascular lesions similar to those occurring in background diabetic retinopathy in humans. These lesions were prevented by treatment with an aldose reductase inhibitor. Aldose reductase inhibitors are becoming increasingly useful in studies related to the possible prevention of diabetic retinopathy. The possible mechanisms involved in endothelial cell proliferation and subsequent pathologies will be investigated using cell culture.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00003-16 LMOD

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)
Pharmacology of Ocular Complications

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Peter F. Kador	Ph.D.	Research Chemist	LMOD, NEI
Others:	Laure Caspers-Velu	M.D.	Visiting Scientist	LMOD, NEI
	Hitoshi Ikebe	M.D.	Visiting Scientist	LMOD, NEI
	Toshihiro Nakayama	Ph.D.	Visiting Scientist	LMOD, NEI
	Sanai Sato	M.D.	Visiting Associate	LMOD, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Mechanisms of Ocular Diseases

SECTION
Section on Molecular Pharmacology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.1	4.1	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Events leading to the onset of various ocular complications are being investigated. Specifically, the role of the enzymes aldose reductase and aldehyde reductase in the onset and progression of retinopathy, cataract, keratopathy, pupil function changes, and iris and ciliary process structure changes associated with diabetes and galactosemia are being studied. Methods to either delay or prevent the onset and progression of these complications through the pharmacological control of these enzymes are being developed.

Events that lead to the formation of several types of cataracts are also being studied. Pharmacological intervention to control the onset of these cataracts is under investigation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00238-04 LMDB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Proto-oncogene Expression During Lens Differentiation and Development

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Peggy Zelenka	Ph.D.	Geneticist	LMDB, NEI
Others:	Michael Berman	Ph.D.	Special Volunteer	LMDB, NEI
	Howard Beswick	Ph.D.	Visiting Fellow	LMDB, NEI
	Sharon Magill		Special Volunteer	LMDB, NEI
	Luke Pallansch	Ph.D.	Staff Fellow	LMDB, NEI
	John Talian	Ph.D.	IRTA Fellow	LMDB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Molecular and Developmental Biology

SECTION

Section on Cellular Differentiation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.38	3.17	0.21

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project investigates the expression of proto-oncogenes during the differentiation of embryonic lens epithelial cells to form lens fiber cells and seeks to determine the specific function of the corresponding gene products in the developing lens. Measurements of steady-state mRNA levels and nuclear run-on transcription experiments have identified several proto-oncogenes which are actively expressed in the embryonic lens. Among these are the nuclear proto-oncogenes, c-myc, c-fos, and p53, and the membrane-associated tyrosine-specific protein kinase, c-src. A transient increase in the expression of the c-myc gene has been found during the early stages of lens fiber cell formation, both in vivo and in vitro, suggesting that this proto-oncogene may be involved in some aspect of differentiation. The increased expression of c-myc is regulated by post-transcriptional as well as transcriptional mechanisms and is closely correlated with changes in expression of the heat shock protein gene HSP70.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00251-02 LMDB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Regulation of the α A-Crystallin Promoter and Its Use for Genetically Engineering the Lens

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Ana B. Chepelinsky	Ph.D.	Research Biologist	LMDB, NEI
Others:	Eric F. Wawrousek	Ph.D.	Staff Fellow	LMDB, NEI
	Joan B. McDermott	M.S.	Biologist	LMDB, NEI
	Joram Piatigorsky	Ph.D.	Chief	LMDB, NEI
	Teresa I. Limjoco	M.D.	Visiting Fellow	LMDB, NEI

COOPERATING UNITS *(if any)*

Gerontological Research Unit, National Institute of Health and Medical Research, Paris, France (Yves Courtois, Ph.D., Maryvonne Laurent, Ph.D.); Imperial Cancer Research Fund, London, England (Clive Dickson, Ph.D., Susan Jamieson, Ph.D.)

LAB/BRANCH

Laboratory of Molecular and Developmental Biology

SECTION

Section on Molecular Genetics

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.7	1.7	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Characterization of the cis-regulatory elements of the murine α A-crystallin promoter responsible for the lens specific expression of this gene and for its developmental regulation continues. The lines of transgenic mice that were generated contain murine α A-crystallin promoter sequences (-111 to +46, -88 to +46 and -34 to +46) fused to the bacterial chloramphenicol acetyltransferase (CAT) gene. The expression of the CAT gene was analyzed. The results indicated that sequence -88 to +46 of the murine α A-crystallin gene contains the cis regulatory elements required for lens-specific expression and for correct developmental regulation of this gene in vivo. Sequence -88 to -35 contains an important regulatory element similar to the one already characterized in chicken lens explants (-88 to -60). The α A-crystallin promoter (-366/+46) has become a very useful tool to target gene expression to the lens and is being used to study how foreign gene expression in the lens affects the phenotype of the lens or the rest of the eye.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00253-01 LMDB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Regulation of Expression of Lens Fiber Membrane-Specific Genes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Ana B. Chepelinsky	Ph.D.	Research Biologist	LMDB, NEI
Others:	M. Michele Pisano	Ph.D.	Staff Fellow	LMDB, NEI
	Thomas R. Chang	B.S.	Summer Student	LMDB, NEI
	Gabriela M. Tobal		Summer Student	LMDB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Molecular and Developmental Biology

SECTION
Section on Molecular Genetics

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

By screening a human leukocyte genomic library with a bovine cDNA clone (Gorin et al. *Cell* 1984 39:49), we have cloned the human MIP (major intrinsic protein) gene. Hybridization experiments indicate that the 16 kbp genomic clone contains 5' and 3' coding regions and noncoding regions, suggesting that it contains the whole gene. The *cis* regulatory elements responsible for the lens-specific expression of this gene will be analyzed by studying the expression of a reporter gene in transient assays under the control of noncoding sequences of the human MIP gene. The cloning of the mouse MIP gene from a mouse genomic library is in progress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00254-01 LMDB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)

Regulatory Elements of the Opsin Promoter

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Ana B. Chepelinsky	Ph.D.	Research Biologist	LMDB, NEI
Others:	Teresa I. Limjoco	M.D.	Visiting Fellow	LMDB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Molecular and Developmental Biology

SECTION

Section on Molecular Genetics

INSTITUTE AND LOCATION

NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.35	0.35	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We are studying the human opsin promoter in transgenic mice. To map the *cis* regulatory elements responsible for opsin gene expression in rod photoreceptor cells, fusion genes containing either 1,000 or 600 bp of sequence flanking the 5' region of the opsin gene has been placed upstream of the bacterial chloramphenicol acetyl transferase (CAT) gene. A hybrid gene containing 200 bp of 5' flanking and 40 bp of exon 1 of the human opsin gene (Nathans and Hogness, *Proc Natl Acad Sci USA* 1984;81:4851) fused to the CAT gene was microinjected into fertilized mouse eggs and several live births are being analyzed to determine whether the injected gene has become integrated into the mouse genome.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00126-08 LMDB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)

Crystallin Genes: Structure, Organization, Expression, and Evolution

PRINCIPAL INVESTIGATOR (*List other professional personnel below the Principal Investigator.*) (*Name, title, laboratory, and institute affiliation.*)

PI:	Joram Piatigorsky	Ph.D.	Chief	LMDB, NEI
Others:	David M. Donovan	Ph.D.	IRTA Fellow	LMDB, NEI
	Robert A. Dubin	Ph.D.	Staff Fellow	LMDB, NEI
	Cynthia Jaworski	M.S.	Chemist	LMDB, NEI
	John F. Klement	Ph.D.	Staff Fellow	LMDB, NEI

COOPERATING UNITS (*if any*)

See next page

LAB/BRANCH

Laboratory of Molecular and Developmental Biology

SECTION

Section on Molecular Genetics

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
10.4	10.4	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (*Use standard unreduced type. Do not exceed the space provided.*)

This laboratory has continued to study crystallin gene expression in the eye lens. Experiments identified positions -88 to -32 in the mouse and -163 to -121 in the chicken αA-crystallin genes as essential for lens-specific promoter function. Additional experiments pinpointed approximately 10 base pairs within these regions of special interest. In collaborative experiments, a cDNA clone encoding a protein binding to the mouse promoter in this region was isolated. Studies on the human αA-crystallin gene identified a sequence similar to the insert exon of rodents. This sequence accumulated a number of mutations, indicating that it has become a pseudo-exon. The mouse α B-crystallin gene was shown to be necessary and sufficient for expression in lens and skeletal muscle. The sequences for the mouse and human α B-crystallin genes have been nearly completed, and the human gene has been mapped to chromosome 11 q.22.3-23.1. The chicken β B1-crystallin promoter was analyzed: the sequence -151/+30 was shown to contain information for lens-specific promoter function. It contains two immunoglobulin-like octomer motifs and a polyoma enhancer-like motif, as well as two potential Sp1 sites. Gel retardation, footprinting and mutagenesis experiments suggested functional significance for at least the octomer and polyoma enhancer-like motifs. Studies on δ-crystallin showed that both genes contain functionally similar promoters and enhancers, yet the δ 1 gene appears lens specific while the δ 2 gene is expressed in the lens, brain, and probably other tissues in chickens. The vimentin gene promoter was shown to contain both positive and negative regulatory elements. Post-transcriptional processes also appear to contribute to a changing pattern of vimentin mRNA in the developing chicken lens. Finally, a jellyfish eye cDNA library was made and it is being screened for the J1-crystallin discovered last year.

Cooperating Units

Section on Mammalian Gene Regulation, Laboratory of Molecular Genetics, National Institute of Child Health and Human Development (Heinreich Westphal, M.D., Head); Section on Molecular Genetics of Immunity, Laboratory of Developmental and Molecular Immunity, National Institute of Child Health and Human Development (Keiko Ozato, Ph.D., Head); Jules Stein Eye Institute, UCLA Medical School, Los Angeles, CA (J. Bronwyn Bateman, M.D.); Medical College of Virginia, Richmond, VA (Z. Zehner, Ph.D.); Jules Stein Eye Institute, UCLA, Medical School, Los Angeles, CA (J. Horwitz, Ph.D.)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00255-01 LMDB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)

Origins, Structures and Functions of Crystallins

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Graeme J. Wistow	Ph.D.	Visiting Associate	LMDB, NEI
Others:	Thomas Lietman	B.A.	HH Medical Student	LMDB, NEI
	Andrea Anderson	B.A.	Guest Worker	LMDB, NEI
	Joram Piatigorsky	Ph.D.	Chief	LMDB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Molecular and Developmental Biology

SECTION

Section on Molecular Genetics

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.55	2.15	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Far from being inert structural proteins, the crystallins, the major components of the ocular lens, are either identical to enzymes or derived from housekeeping or stress-related proteins. The gene for α-enolase/τ–crystallin from the duck has been cloned and sequenced and experiments to determine the mechanisms of its high expression in lens have begun. In the case of another enzyme-crystallin, argininosuccinate lyase/δ-crystallin, it is apparent that great variability is tolerated in lens. Two genes are expressed in some lenses with high enzyme activity while the perfectly transparent lenses of the swift have no δ-crystallin at all. In the swift and the related hummingbird, δ-crystallin is entirely or almost entirely replaced by ε-crystallin lactate dehydrogenase B. Early mammals may also have made use of enzyme-crystallins. In the primitive elephant shrew, η-crystallin/aldehyde dehydrogenase almost completely replaces γ-crystallin just as δ-crystallin does in birds. The same strategy has been used in two different lines of descent but with a different choice of enzyme. The relationships between crystallins and housekeeping or stress proteins have been extended by the discovery of structural similarity between β- and γ-crystallins and spherulin 3a, a dormancy protein in *Physarum polycephalum.*

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00070-12 LRCMB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)
Vitamin A and Ocular Tissues

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Barbara Wiggert	Ph.D.	Head, Section on Biochemistry	LRCMB, NEI
Others:	Ling Lee	M.S.	Chemist	LRCMB, NEI
	Michael Redmond	Ph.D.	Staff Fellow	LRCMB, NEI
	Gerald J. Chader	Ph.D.	Director of Intramural Research	NEI

COOPERATING UNITS *(if any)*
See next page

LAB/BRANCH
Laboratory of Retinal Cell and Molecular Biology

SECTION
Section on Biochemistry

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.5	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Interphotoreceptor retinoid binding protein (IRBP) was studied in retinae of miniature poodles with progressive rod-cone degeneration (prcd) and Abyssinian cats homozygous for the retinal degeneration gene. In the affected poodle retina, IRBP was reduced in the inferior quadrants by 2 years of age, correlating with more severe disease and degeneration in these quadrants. IRBP could be detected by immunocytochemistry until photoreceptor inner segments were lost. In the affected cat retina, IRBP was significantly reduced at an early stage of the disease before any marked loss of photoreceptor cells.

In cultures of isolated mouse photoreceptor cells, the expression of IRBP immunoreactivity was associated exclusively with photoreceptor cells and was developmentally regulated. The IRBP appeared to be loosely bound to the photoreceptor cell surface and in equilibrium with IRBP in the culture medium. Less IRBP was secreted into the medium by rd/rd photoreceptor cells, confirming our earlier result indicating a defect in IRBP secretion by rd/rd photoreceptor cells.

In studies of the induction of experimental autoimmune uveoretinitis by IRBP in the Lewis rat, synthetic peptides were used to establish that IRBP contains two immunodominant and immunopathogenic determinants which are cross-reactive.

Purified bovine IRBP was able to transfer 11-cis retinal to bleached rod photoreceptor cells from larval tiger salamander (*Ambystoma tigrinium*) and could also reverse deleterious effects of 11-cis retinol by removing the retinoid from the rod cells.

Cooperating Units

Boston University School of Medicine, Boston, MA (C. Cornwall, G. Jones); The Johns Hopkins University, Baltimore, MD (R. Adler); University of Lund, Lund, Sweden (T. van Veen); University of Illinois College of Medicine, Chicago, IL (D. Pepperberg, H. Ripps); University of Pennsylvania School of Veterinary Medicine, Philadelphia, PA (G. Aguirre, K. Long)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00015-24 LRCMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)

The Cell Biology of the Vertebrate Retina

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Paul J. O'Brien	Ph.D.	Head, Section on Cell Biology	LRCMB, NEI
Others:	Sylvia B. Smith	Ph.D.	IRTA Fellow	LRCMB, NEI
	Caren C. Demars	B.A.	Biologist	LRCMB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Retinal Cell and Molecular Biology

SECTION

Section on Cell Biology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.8	0.7	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The post-translational modifications of rhodopsin include acylation, glycosylation, and chromophore addition. All appear to take place in the rod inner segment. The resulting molecules exhibit a slightly higher molecular weight than the mature rhodopsin in the outer segment and thus can be distinguished. The role of the palmitate residues is unknown but could be related to membrane assembly. The addition of the vitamin A chromophore seems to be essential for intracellular transport of the opsin protein to the Golgi and to the outer segments. The addition of several sugar residues in the Golgi complex may be a requirement for normal outer segment disc formation since the rhodopsin molecules in the plasma membrane and basal folds have a higher molecular weight than rhodopsin in disc membranes.

Rod outer segments contain a molecule with both inositol and glucosamine. This molecule is reminiscent of the phosphatidylinositol-glycan anchor found in transiently membrane-bound proteins and may indicate the existence of a phospholipase-mediated release mechanism.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00016-22 LRCMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Biochemistry of Normal and Dystrophic Retinas

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Paul J. O'Brien	Ph.D.	Head, Section on Cell Biology	LRCMB, NEI
Others:	Sylvia B. Smith	Ph.D.	IRTA Fellow	LRCMB, NEI
	Caren C. Demars	B.A.	Biologist	LRCMB, NEI

COOPERATING UNITS *(if any)*

School of Veterinary Medicine, University of Pennsylvania (G. Aguirre); Cullen Eye Institute, Baylor College of Medicine (R.E. Anderson)

LAB/BRANCH

Laboratory of Retinal Cell and Molecular Biology

SECTION

Section on Cell Biology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.8	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies on phospholipid metabolism were conducted using a variety of labeled precursors such as fatty acids and glycerol. These precursors were either incubated with dog retinas or injected into dog eyes 1 day before enucleation. A comparison was made between the retinas of normal poodles and those affected with progressive rod-cone degeneration, an inherited disorder closely resembling retinitis pigmentosa in humans. No differences were noted between the normal and affected retinas. However, the essential fatty acid, linolenic acid, having 18 carbon atoms and 3 double bonds, was not elongated and desaturated by the retina to docosahexaenoic acid with 22 carbons and 6 double bonds. This fatty acid is uniquely enriched in photoreceptor disc membranes and must be made by the liver from dietary sources of linolenic acid. Blood from affected dogs exhibited abnormally low levels of docosahexaenoic acid, as did their photoreceptor disc membrane phospholipids. Thus, a systemic defect in fatty acid metabolism is reflected in a retinal disorder based on the retina's unusually high demand for docosahexaenoic acid.

Similarly, low blood levels of docosahexaenoic acid are found in some autosomal dominant and X-linked retinitis pigmentosa patients, as well as in those with Usher's syndrome.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00124-09 LRCMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Metabolism of the Retina and Pigment Epithelium

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Gerald J. Chader	Ph.D.	Director of Intramural Research	NEI
Others:	Robert Waldbillig	Ph.D.	Expert	LRCMB, NEI
	R. Theodore Fletcher	M.S.	Chemist	LRCMB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Retinal Cell and Molecular Biology

SECTION

Section on Gene Regulation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.7	1.2	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Low-molecular-weight soluble factors play major roles in the growth and development of all tissues. These messengers and hormones affect both normal and abnormal growth and metabolism within a tissue. Insulin and insulin-like growth factor-1 (IGF-1) may act as messengers, coding for differentiation in the retina and, by affecting phosphorylation of the G-protein transducin, may be directly or indirectly involved in the visual process in the adult animal. Of equal importance, receptors for these messengers found in high concentration in developing retina, pigment epithelium, and sclera may play a role in differentiation of these tissues. Abnormal ocular growth during experimental myopia has been found to be associated with changes in insulin and IGF-1 receptor binding.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00148-16 LRCMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Visual Control Mechanisms

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Gerald J. Chader	Ph.D.	Director of Intramural Research	NEI
Others:	R. Theodore Fletcher	M.S.	Chemist	LRCMB, NEI
	Lila Inouye	M.D.	Staff Fellow	LRCMB, NEI
	Betty J. Hayden	Ph.D.	Staff Fellow	LRCMB, NEI

COOPERATING UNITS *(if any)*

School of Veterinary Medicine, University of Pennsylvania (G. Aguirre); Department of Anatomy, Erasmus University, Rotterdam, The Netherlands (S. Sanyal); Department of Zoology, University of Lund, Lund Sweden (T. van Veen)

LAB/BRANCH

Laboratory of Retinal Cell and Molecular Biology

SECTION

Section on Gene Regulation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.2	1.7	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Several hereditary diseases strike the neural retina. Among these are retinitis pigmentosa and retinoblastoma. There may be important genes and their protein products that are specific to the retina and abnormal either in function or concentration in these retinal diseases. We are studying polymorphic DNA in a progressive rod-cone degeneration canine pedigree to tag animals with the degeneration. We also are investigating putative homology of fruitfly genomic sequences to interphotoreceptor retinoid-binding protein (IRBP) to pinpoint possible involvement of IRBP in one or more of the known visual mutants in *Drosophila.* In a third study, we have found that a specific cAMP-dependent protein kinase exhibits a defect in synthesis in retinoblastoma tumor cells. Such a defect could cause the uncontrolled growth of retinoblastoma cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00196-06 LRCMB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Molecular Genetics of the Eye and Ocular Diseases

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	John M. Nickerson	Ph.D.	Biologist	LRCMB, NEI
Others:	Diane Borst	Ph.D.	IRTA Fellow	LRCMB, NEI
	T. Michael Redmond	Ph.D.	Staff Fellow	LRCMB, NEI
	Jing-Sheng Si	M.D.	Visiting Associate	LRCMB, NEI
	David Saperstein	M.D.	Extramural NRSA	LRCMB, NEI

COOPERATING UNITS *(if any)*
Wilmer Eye Institute, The Johns Hopkins University, Baltimore, MD (R. Adler); University of Maryland Medical School, Baltimore, MD (M. Rodrigues); Jules Stein Eye Institute, UCLA, Los Angeles, CA (D. Farber, B. Bateman, J. Ngo-Jones, R. Sparkes); Zoology Department, University of Lund, Lund, Sweden (Theo van Veen)

LAB/BRANCH
Laboratory of Retinal Cell and Molecular Biology

SECTION
Section on Gene Regulation

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.2	3.2	

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

IRBP is the first example of an extracellular matrix protein that plays a role in transporting, buffering, or mediating the actions of retinoids and fatty acids in the interphotoreceptor space. This laboratory has isolated and characterized recombinant DNA molecules (both full-length cDNAs and complete genes) necessary for the study of the structure and expression of IRBP. We have determined the primary structure of the IRBP gene and its protein. These data are invaluable and an absolute prerequisite to advanced and thorough study of IRBP gene expression. The DNA clones are important substrates that, when altered or manipulated, provide the tools for studies of the synthesis and function of IRBP. The polypeptide contains four 300-amino-acid- long repeats, with 30% to 40% identity among the repeats. These sequences have been helpful in the analysis of the uveitogenic peptides in IRBP. We have identified the authentic N-terminus, the putative initiator methionine codon, a putative propeptide and a putative signal peptide sequence of the IRBP polypeptide. In addition, we have determined the size and cellular location in the retina of the IRBP mRNA. The IRBP mRNA is long, 4.4 to 7.4 kb in several species, and usually gives only one band on a northern blot. We have analyzed the IRBP gene in many species, especially human. We have determined that there is only one IRBP gene per haploid genome. The chromosomal location of the IRBP gene is 10 for human, 4 for dog, and 14 for mouse. The IRBP gene structure is compact for the size of the protein, and it has only three introns. The remarkable quadruplication within the gene suggests an interesting evolution, possibly involving a processed gene intermediate and two unequal crossovers

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00132-08 LRCMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Molecular Biology of Phototransduction

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Toshimichi Shinohara	Ph.D.	Head, Section on Molecular Biology	LRCMB, NEI
Others:	Masahiko Tsuda	M.D., Ph.D.	Visiting Associate	LRCMB, NEI
	Kunihiko Yamaki	M.D., Ph.D.	Visiting Associate	LRCMB, NEI
	Tohru Abe	M.D., Ph.D.	Visiting Associate	LRCMB, NEI
	Vijay K. Singh	Ph.D.	Visiting Associate	LRCMB, NEI

COOPERATING UNITS *(if any)*

Jules Stein Eye Institute, UCLA Medical School (Julielani T. Ngo, J. Bronwyn Bateman, Michael Danciger and Debora B. Farber)

LAB/BRANCH

Laboratory of Retinal Cell and Molecular Biology

SECTION

Section on Molecular Biology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.1	3.1	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Using recombinant DNA technologies, we have characterized S-antigen from human, mouse, bovine, and rat tissue, as well as human rhodopsin kinase, rat and human 32K protein, and human 24K ROS specific proteins. All of these proteins are present in photoreceptor rod cells. S-antigen cDNA sequences have been determined by DNA sequence determination methods and the deduced amino acid sequences have local regions of sequence homology with alpha-transducin. The sequence of S-antigen present in the pineal and retina is virtually identical. This result suggests that the function of S-antigen is identical in both tissues.

Rhodopsin kinase (RK) belongs to a family of proteins which have conserved features and similar catalytic domains among themselves. Using catalytic domain DNA probes, RK cDNA was isolated from human retinal cDNA libraries, and its sequence was determined. The deduced amino acid sequence had a sequence characteristic of known kinases. An antibody against a synthetic oligo-peptide of the deduced RK bound to a 68 kD protein is present only in retina.

The 24K and 32K ROS specific proteins have no sequence similarity with other known proteins. Thus, the amino acid sequences of these proteins further substantiated their functional roles in the phototransduction cascade. The mouse S-antigen gene sequence was determined. It has 15 introns and 16 exons in a 50 kbp length of DNA. The S-antigen gene is mapped to chromosome No. 1 in mouse and chromosome No. 2 in humans. We have constructed fusion genes containing 5' flanking opsin gene sequence upstream of the bacterial gene chloramphenicol acetyl transferase (CAT). A hybrid gene containing 200, 600, and 1,000 bp of 5' flanking and 40 bp of exon of the human opsin gene fused to the CAT gene was microinjected into fertilized mouse and tested for tissue-specific expression of CAT gene in transgenic mouse system.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00250-02 LRCMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Molecular Biology of Experimental Autoimmune Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Toshimichi Shinohara	Ph.D.	Head, Section on Molecular Biology	LRCMB, NEI
Others:	Kunihiko Yamaki	M.D., Ph.D.	Visiting Associate	LRCMB, NEI
	Vijay K. Singh	Ph.D.	Visiting Associate	LRCMB, NEI
	Masahiko Tsuda	M.D., Ph.D.	Visiting Associate	LRCMB, NEI
	Tohru Abe	M.D., Ph.D.	Visiting Associate	LRCMB, NEI

COOPERATING UNITS *(if any)*

Wills Eye Hospital, Philadelphia, PA (Larry A. Donoso, M.D., Ph.D.)

LAB/BRANCH

Laboratory of Retinal Cell and Molecular Biology

SECTION

Section on Molecular Biology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.9	1.9	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This laboratory has determined amino acid sequences of human, mouse, and bovine retinal S-antigen and rat pineal gland S-antigen. Immunogenic sites and four uveitopathogenic sites of S-antigen were also determined. Many proteins in the National Biomedical Research Foundation data base have similar sequences with uveitopathogenic site. We induced EAU and pinealitis in Lewis rats with a small synthetic peptide from yeast (*Saccharomyces cerevisiae*) histone H3, which contains five consecutive amino acids identical to a uveitopathogenic site in human S-antigen. Synthetic peptides of proteins from potato proteinase inhibitor, hepatitis virus, Moloney murine sarcoma virus, and Moloney murine leukemia virus also induced EAU. In addition, native yeast histone H3 was capable of inducing EAU. These findings provide a basis for understanding human autoimmune inflammatory diseases of the eye.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00256-01 LSR

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Information Processing by Visual System Neurons

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	L. M. Optican	Head, Section on Neural Modeling	LSR, NEI
Others:	J. W. McClurkin	Staff Fellow	LSR, NEI
	P. J. Joseph	Engineering Contractor	LSR, NEI
	B. J. Richmond	Senior Investigator	LNP, NIMH
	T. J. Gawne	Staff Fellow	LNP, NIMH

COOPERATING UNITS *(if any)*

Air Force Office of Scientific Research

LAB/BRANCH

Laboratory of Sensorimotor Research

SECTION

Section on Neural Modeling

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.8	1.9	0.9

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Visual perception depends on the rich interactions among individual neurons. These interactions depend on mechanisms that encode, process, and transmit information among different visual areas of the brain. Neurophysiological methods observe the consequences of this information processing, but have not yet provided an understanding of its underlying mechanisms. We are applying information theory to provide a foundation for such an understanding by quantifying the encoding and transmission of information by neurons.

The current work studies the ability of neurons in different areas of the brain to encode and transmit information about stationary, two-dimensional pictures that vary in form, brightness, and duration. Neurophysiological data have been analyzed using our new, unbiased method of computing information. In all areas studied, the neurons encode picture information using a multidimensional temporal code. Neurons can transmit at least 3 times as much information using a multivariate temporal code as could be transmitted using a univariate strength code. The temporal code has a relatively long duration, between 100 and 300 msec. We have established that feedback from the next cortical area contributes to this temporal modulation. Moreover, in response to a change in the stimulus picture, a new temporal message is established within 30 msec. Also, the amount of information assigned to the temporal waveform increases, relative to that assigned to the response strength alone, as the signals pass from the retina to the inferior temporal cortex. Finally, different stimulus parameters (form, brightness, duration) are encoded in a separable way, so that they are not confounded. These results suggest that temporal modulation is an important mechanism for processing visual information. Its study may contribute to the understanding of visual perception.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00244-02 LSR

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Oculomotor and Visual Disorders in Humans

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	James R. Carl	M.D.	Expert	LSR, NEI
Others:	Edmond J. FitzGibbon	M.D.	Senior Staff Fellow	LSR, NEI
	Michael E. Goldberg	M.D.	Chief, NMS	LSR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Sensorimotor Research

SECTION
Section on Neuro-Ophthalmologic Mechanisms

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.4	1.4	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Humans with a variety of oculomotor and visual problems were evaluated with clinical examinations and high resolution eye movement recordings. Patients with cerebellar disease were evaluated for amount and type of clinical abnormality and the eye movements in response to stimuli testing the oculomotor sub-systems were correlated with the clinical findings. Patients with nystagmus and with supra-nuclear disorders of gaze were similarly tested to develop diagnostic criteria for disease classification and evaluation of therapy. Smooth pursuit asymmetry was analysed in patients for evidence of cortical motion processing abnormalities.

Patients enrolled in mevinolin drug trials were tested for evidence of cataract and visual dysfunction, and patients receiving intra-arterial BCNU were screened for toxicity. One patient developed retinal neovascularization, a finding previously unreported.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00049-11 LSR

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cerebral Cortical Mechanisms for Eye Movements and Visual Attention

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Michael Goldberg	M.D.	Head, Section on Neuro-Ophthalmologic Mechanisms	LSR, NEI
Others:	Edmond J. FitzGibbon	M.D.	Senior Staff Fellow	LSR, NEI
	Carol L. Colby	Ph.D	Senior Staff Fellow	LSR, NEI
	Jean-Rene Duhamel	Ph.D.	Visiting Scientist	LSR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Sensorimotor Research

SECTION
Section on Neuro-Ophthalmologic Mechanisms

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.3	2.2	1.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Two different lines of inquiry were followed to determine how the cerebral cortex and its efferent regions control eye movements and visuospatial attention.

In one, the activity of neurons in the intermediate layers of the superior colliculus was studied during the process of saccadic adaptation. Visual neurons in the area do not change their receptive fields. Movement neurons appear to change their movement during the process of adaptation, but only if the visual stimulus to which the adapted saccade is made remains constant. This implies that the signal coded by the movement neurons of the superior colliculus is the visual location of the target, not the motor signal necessary to acquire the target.

In the other, visual neurons in the posterior parietal cortex were studied using double-step tasks to see how this cortex might maintain spatial accuracy when there was dissonance between the retinal location of a stimulus and the saccade necessary to acquire that stimulus. Neurons in this region discharged when the monkey made a saccade of the proper direction to acquire a stimulus, whether or not that stimulus lay in the neuron's receptive field as studied in a routine fixation task. Such neurons required the presence of a visual stimulus, which suggests posterior parietal cortex spatial accuracy is maintained by coordinate transformation of a visual map rather than explicit coding of a target's position in space.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00153-07 LSR

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Visual Motion and the Stabilization of Gaze

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Frederick A. Miles	Ph.D.	Head, Section on Oculomotor Control	LSR, NEI
Others:	Hubert Kimmig	M.D.	Visiting Fellow	LSR, NEI
	Urs Schwarz	M.D.	Visiting Fellow	LSR, NEI
	Thomas S. Collett	Ph.D.	Visiting Scientist	LSR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Sensorimotor Research

SECTION

Section on Oculomotor Control

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.6	1.0	0.6

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Eye movements exist to improve vision, in part by preventing excessive retinal image slip. A major threat to the stability of the retinal image comes from the observer's own movement. There are visual and vestibular reflexes that operate to meet this challenge by generating compensatory eye movements. Using monkeys, we have recorded the ocular responses to translational disturbances of the observer and of the scene, finding that the associated vestibular and visual responses are both linear functions of the inverse of the viewing distance. Such dependence on proximity is appropriate for the vestibular reflex, which must transform signals from cartesian to polar coordinates, but not for the visual reflex, which operates entirely in polar coordinates. However, such shared proximity effects in the visual reflex could compensate for known intrinsic limitations that would otherwise compromise performance at near viewing. Other experiments indicate that the vestibular responses could be increased by selectively increasing either vergence (using base-out prisms and distant targets) or accommodation (using base-in prisms and near targets), the increases in response being similar in the two cases. These data indicate that the vestibular reflex uses some internal measure of both the vergence and the accommodative states to modulate its gain in accordance with the viewing distance.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: ZO1 EY 00045-11 LSR

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Visuomotor Properties of Neurons in the Thalamus

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	David Lee Robinson	Ph.D.	Research Physiologist	LSR, NEI
Others:	Caroline Kertzman	Ph.D.	IRTA	LSR, NEI
	Richard Sherins	M.D.	Res. Endocrinologist	NICHD
	Irene Litvan	M.D.	Clinical Fellow	NINCDS
	Edmond FitzGibbon	M.D.	Sr. Staff Fellow	LSR, NEI
	James Carl	M.D.	Sr. Staff Fellow	LSR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Sensorimotor Research

SECTION

Section on Visual Behavior

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.4	0.6

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Research in this section has been directed toward understanding the perceptual and neuronal basis of visual spatial attention. Reaction times for responding to peripheral targets are faster if they are preceded by visual cues located in the same areas of space than if the targets are preceded by cues at other locations. The differences in reaction times are hypothesized to reflect the effects of spatial attention. In normal humans, spatial attentional performance is very stable and not influenced by gender, age, motivation, or status of the menstrual cycle. However, when cues for directing attention are not present, attentional abilities are slower in females, decrease with age, and fluctuate with the menstrual cycle.

The integrity of parietal cortex is essential for the task of directing attention in humans and monkeys. By recording from neurons while monkeys performed this paradigm, we have shown that just as reaction time performance is influenced by various cuing conditions, the discharge of parietal neurons is affected by the cuing. Parietal cells' response is less to targets preceded by cues in the same visual area than to targets preceded by cues in other regions. This reduction in response diminishes with increasing time intervals between cue and target.

In other behavioral situations, we have demonstrated the spatial and temporal characteristics of attentional effects on parietal cells. These may be the mechanisms which the parietal lobe uses in modulating visual perception. There are improvements in visual perception and visuomotor processing just after a saccadic eye movement. When we tested the excitability of neurons in the pulvinar around the time of eye movements, many showed facilitated responsiveness. For some of these cells, the augmentation is related to the position of the eye. For others, the effect is associated with the eye movement itself. For all cells tested, these changes are present with the animal in the dark. This suggests that visuo-visual interactions do not account for these changes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: ZO1 EY 00109-09 LSR

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)

Visuomotor Processing in the Primate Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Robert H. Wurtz	Ph.D.	Chief	LSR, NEI
Others:	Dwayne S.G. Yamasaki	Ph.D.	Staff Fellow	LSR, NEI
	Jean-Pierre Roy	M.D., Ph.D.	Guest Researcher	LSR, NEI
	Charles J. Duffy	M.D., Ph.D.	Staff Fellow	LSR, NEI
	David M. Waitzman	M.D., Ph.D.	Staff Fellow	LSR, NEI
	Terence P. Ma	Ph.D.	Guest Researcher	LSR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Sensorimotor Research

SECTION

Section on Visuomotor Integration

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.9	3.1	1.8

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Our experiments have concentrated on two aspects of visuomotor processing in the brain, the generation of eye movements, and movement through the environment. One set of studies focused on the response of cells in the superior colliculus with relationship to saccadic eye movements. We found that two general types of cells, each having different dynamic responses, respond during saccadic eye movements. These eye movements, made under a variety of behavioral conditions, may occur spontaneously in the dark or in response to visual targets or to targets that had to be remembered. That different cell types participate in different types of saccades suggests that the superior colliculus is a site of convergence for commands from different sources.

Another set of experiments concentrated on visual motion processing in the medial superior temporal (MST) area of the cerebral cortex, in which we found cells that were responsive to optic flow stimuli. These stimuli contained the radial-type motion that is observed as we move through a visual environment. We also found that cells in MST are sensitive to disparity; they convey information about depth by having receptive fields at slightly different positions in the retinas of the two eyes. These cells' sensitivity to disparity was primarily for objects close to the observer (near cells) or far from the observer (far cells). This combination of optic flow and disparity characteristics is consistent with the use of visual information in this area to determine the depth of objects in the environment and possibly the motion of the subject through the environment.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00062-13 OGCSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Irido-Corneal-Endothelial (ICE) Syndrome

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Manuel B. Datiles	M.D.	Visiting Scientist	OGCS, NEI
Others:	Muriel I. Kaiser-Kupfer	M.D.	Chief, Ophthalmic Genetics and Clinical Services Branch	NEI
	Paul A. Edwards	M.D.	Visiting Fellow	OGCS, NEI
	Lessie McCain	R.N.	Clinical Technician	OGCS, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Ophthalmic Genetics and Clinical Services Branch

SECTION
Section on Cataract and Corneal Diseases

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.3	0.2	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project was formerly titled "Progressive Essential Iris Atrophy." Patients with progressive essential iris atrophy with or without associated corneal disease are being recruited. Information is being gathered to evaluate the clinical features and course of the disease process and to investigate aqueous humor dynamics in both affected and unaffected eyes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
ZO1 EY 00187-06-OGCSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Effects of Corneal Contact Lenses on the Cornea

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Manuel B. Datiles	M.D.	Visiting Scientist	OGCS, NEI
Others:	Mariel E. Sibug	M.D.	Visiting Fellow	OGCS, NEI
	Lessie McCain	R.N.	Clinical Technician	OGCS, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Ophthalmic Genetics and Clinical Services Branch

SECTION
Section on Cataract and Corneal Diseases

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.2	0.1	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Short-term as well as long-term effects of contact lens wear on the cornea are being investigated. Changes in corneal curvature, changes in corneal epithelial morphology, and changes in corneal endothelial cell morphology are being studied by specular microscopy.

Analysis of the data obtained will help us understand the dynamics involved in the interaction between a contact lens and the cornea, the risk to corneal tissues, and how a systemic or local disorder may increase these risks.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00188-06 OGCSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Documentation and Monitoring of Opacities in the Human Lens

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Manuel B. Datiles	M.D.	Visiting Scientist	OGCS, NEI
Others:	Rafael C. Caruso	M.D.	Visiting Scientist	OGCS, NEI
	Paul A. Edwards	M.D.	Visiting Fellow	OGCS, NEI
	Kayako Kashima	M.D.	Visiting Scientist	OGCS, NEI
	James Schumer	M.D.	Staff Fellow	OGCS, NEI
	Mariel E. Sibug	M.D.	Visiting Scientist	OGCS, NEI
	Lessie McCain	R.N.	Clinical Technician	OGCS, NEI

COOPERATING UNITS *(if any)*
Image Processing and Analysis Laboratory, Division of Computer Research and Technology, NIH (Benes Trus, Ph.D., Chief); Clinical and Diagnostic Trials Section, National Cancer Institute, NIH (Sylvan Green, M.D.); Nuclear Medicine, Clinical Center, NIH (Joseph Frank, M.D.)

LAB/BRANCH
Ophthalmic Genetics and Clinical Services Branch

SECTION
Section on Cataract and Corneal Diseases

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.3	2.1	0.2

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project uses different systems to develop objective and subjective methods to monitor and document opacities in the human lens. We are actively recruiting patients with and without cataracts for reproducibility studies on the objective systems—the Scheimpflug cameras (Zeiss and Topcon), retroillumination camera (Neitz), specular microscope (Keeler) and laser light-scattering spectroscope (Kowa). We will also test other systems using sound (ultrasonography) and nuclear magnetic resonance (magnetic resonance imaging). We are also studying subjective systems or methods, such as the effects of cataracts on visual perception, contrast sensitivity, and glare that may be useful as additional parameters in monitoring cataract presence, progression, or regression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00212-04 OGCSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)
Model Program for Collaboration Between Cataract Surgeons and Ophthalmic Researchers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Manuel B. Datiles	M.D.	Visiting Scientist	OGCS, NEI
Others:	James Schumer	M.D.	Staff Fellow	OGCS, NEI
	Paul A. Edwards	M.D.	Visiting Fellow	OGCS, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Ophthalmic Genetics and Clinical Services Branch

SECTION
Section on Cataract and Corneal Diseases

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.1	1.1	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

There is an extreme scarcity of human cataract material because of an abrupt shift of cataract surgical technique from intracapsular (intact lens) to extracapsular (fragmented lens), primarily because of the advent of the use of intraocular lens. We are exploring ways by which fragmented lens materials can be used maximally in cataract basic research through close collaboration of cataract surgeons with basic researchers and modification of techniques by both groups.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00084-11 OGCSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)
Anterior Chamber Anomalies Associated with Glaucoma or Ocular Hypertension

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Carl Kupfer	M.D.	Director	NEI
Others:	Muriel I. Kaiser-Kupfer	M.D.	Chief, Ophthalmic Genetics and Clinical Services Branch	NEI
	Lessie McCain	R.N.	Clinical Technician	OGCS, NEI
	Manuel B. Datiles	M.D.	Visiting Scientist	OGCS, NEI
	Paul A. Edwards	M.D.	Visiting Fellow	OGCS, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Ophthalmic Genetics and Clinical Services Branch

SECTION
Section on Cataract and Corneal Diseases

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.65	0.55	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☒ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Recent embryological research has indicated the role of the neural crest in contributing to all connective tissues anterior to the lens epithelium. Therefore, the group of developmental anomalies of the anterior chamber with glaucoma or ocular hypertension is being reviewed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00257-01 OGCSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)
Visual Function Diagnosis Service

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Rafael Caruso	M.D.	Visiting Scientist	OGCS, NEI
Others:	Muriel I. Kaiser-Kupfer	M.D.	Chief, Ophthalmic Genetics and Clinical Services Branch	NEI

COOPERATING UNITS *(if any)*
Center for Sight, Georgetown University, Washington, D.C. (Donna Optican, M.A.S., Despina Koustsandreas, B.S., Amy Pratt, C.O.T., Robert Toma, C.O.T.)

LAB/BRANCH
Ophthalmic Genetics and Clinical Services Branch

SECTION
Section on Clinical Services

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.15	0.15	

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This is a general service project which provides diagnostic support for all research protocols conducted by the Clinical Sections of the National Eye Institute and other Institutes that require an assessment of visual function. Psychophysical and electrophysiological techniques are used to detect and quantify visual loss due to disorders of the ocular media, uvea, retina, optic nerve, and central visual pathways.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00011-15 OGCSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Pigment Dispersion With and Without Glaucoma

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Muriel I. Kaiser-Kupfer	M.D.	Chief, Ophthalmic Genetics and Clinical Services Branch	NEI
Others:	Paul A. Edwards	M.D.	Visiting Fellow	OGCS, NEI
	Lessie McCain	R.N.	Clinical Technician	OGCS, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Ophthalmic Genetics and Clinical Services Branch

SECTION
Section on Ophthalmic Genetics

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.45	0.25	0.2

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to determine the risks of patients with pigment dispersion syndrome to developing glaucoma. Comparisons of patients with and without glaucoma will be made on the basis of diagnostic tests, genetic screening, aqueous humor dynamics, and pupillary responses to light. The data acquired may enable a determination of the risk of patients with pigment dispersion syndrome to developing glaucoma, as well as adding to the understanding of the pathology of the disease.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00060-11 OGCSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)
Visual Function and Ocular Pigmentation in Albinism

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Muriel I. Kaiser-Kupfer	M.D.	Chief, Ophthalmic Genetics and Clinical Services Branch	NEI
Others:	Lessie McCain	R.N.	Clinical Technician	OGCS, NEI
	Rafael Caruso	M.D.	Visiting Scientist	OGCS, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Ophthalmic Genetics and Clinical Services Branch

SECTION
Section on Ophthalmic Genetics

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.2	0.15	0.05

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Patients with hypomelanotic disorders such as ocular albinism, oculocutaneous albinism, Chediak-Higashi disease, Hermansky-Pudlak syndrome, and iris transillumination defects are being recruited to determine visual function with these conditions and to evaluate the changes in visual function course over time. Family members are evaluated to attempt to determine factors which may identify the heterozygous state.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00083-12 OGCSB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Gyrate Atrophy of the Choroid and Retina and Other Retinal Degenerations

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Muriel I. Kaiser-Kupfer	M.D.	Chief, Ophthalmic Genetics and Clinical Services Branch	NEI
Others:	T. Otis Paul	M.D.	Expert	OGCS, NEI
	Michael Gorin	M.D., Ph.D.	Medical Officer	OGCS, NEI
	Lessie McCain	R.N.	Clinical Technician	OGCS, NEI
	Rafael Caruso	M.D.	Visiting Scientist	OGCS, NEI
	Doris Collie	A.A.	Health Technician	OGCS, NEI
	Paul A. Edwards	M.D.	Visiting Fellow	OGCS, NEI

COOPERATING UNITS *(if any)*

The Howard Hughes Medical Institute Laboratory and the Department of Pediatrics, The Johns Hopkins University, School of Medicine, Baltimore, MD (David L. Valle, M.D.)

LAB/BRANCH

Ophthalmic Genetics and Clinical Services Branch

SECTION

Section on Ophthalmic Genetics

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.4	0.9	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Patients with gyrate atrophy of the choroid and retina are examined systematically to confirm the diagnosis. Skin fibroblasts of affected patients and family members are grown in tissue culture and assayed for ornithine aminotransferase activity. The results are evaluated for correlation with the presence of homozygosity or heterozygosity for the disease trait. Patients are given a trial of pyridoxine to see if serum concentration of ornithine can be reduced; if so, the patient is classified as a "responder," and treatment with pyridoxine is continued. Nonresponder and responder patients are then placed on a low arginine, low-protein diet with supplemental amino acids and observed for arrest or improvement of the disease. If patients are not considered eligible for the diet, or if they appear unable to comply with the dietary regimen, they are followed to record the natural progression of the condition. Patients with other forms of retinal degeneration such as retinitis pigmentosa, fundus flavimaculatus, juvenile retinoschisis, Usher's syndrome, etc., are also examined and their courses are compared with those of gyrate atrophy patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
ZO1 EY 00123-09-OGCSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)
Clinical Psychophysics of the Visual System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Muriel I. Kaiser-Kupfer	M.D.	Chief, Ophthalmic Genetics and Clinical Services Branch	NEI
Others:	Rafael C. Caruso	M.D.	Visiting Scientist	OGCS, NEI
	T. Otis Paul	M.D.	Expert	OGCS, NEI
	Michael B. Gorin	M.D., Ph.D.	Medical Officer	OGCS, NEI
	Doris J. Collie	A.A.	Health Technician	OGCS, NEI

COOPERATING UNITS *(if any)*
Georgetown University Center for Sight, Washington, DC (Despina Koutsandreas, B.S., Robert Toma, C.O.T.); The Howard Hughes Medical Institute Laboratory and Department of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, MD (David L. Valle, M.D.)

LAB/BRANCH
Ophthalmic Genetics and Clinical Services Branch

SECTION
Section on Ophthalmic Genetics

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.15	0.85	0.3

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The visual function of patients with ocular diseases or lesions in the visual pathways and of normal subjects is measured by psychophysical techniques. The data obtained are correlated with those obtained by electrophysiological tests of visual function. The results will contribute to the diagnosis of ocular and neural disorders that affect vision and are needed to characterize their nature and evolution. They are also valuable in the assessment of the effect of treatment regimens on the outcome of these diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00163-07 OGCSB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)

NIH Interinstitute Genetics Program: The Genetics Clinic

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Muriel I. Kaiser-Kupfer	M.D.	Chief, Ophthalmic Genetics and Clinical Services Branch	NEI
Others:	Michael B. Gorin	M.D., Ph.D.	Medical Officer	OGCS, NEI
	T. Otis Paul	M.D.	Expert	OGCS, NEI
	Lessie McCain	R.N.	Clinical Technician	OGCS, NEI

COOPERATING UNITS *(if any)*

Interinstitute Medical Genetics Program, NIH

LAB/BRANCH

Ophthalmic Genetics and Clinical Services Branch

SECTION

Section on Ophthalmic Genetics

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.45	0.35	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Interinstitute Genetics Program and the Genetics Clinic, supported by the Clinical Center, offer a multidisciplinary approach to patients with genetic disease (ZO1 CP 05139-04 CEB). Involved in the program are researchers from all Institutes. Patients evaluated in the clinic represent a broad spectrum of genetic diseases. During the last year, the approximately 400 individuals seen represented about 100 distinct disease categories. Due to the high frequency of ocular involvement in many of the cases, almost all the patients were evaluated by Clinical Branch staff or were discussed in consultation. The Clinic serves as a source of interesting case material concerning patients with inherited or developmental abnormalities of the visual system.

In addition to the Genetics Clinic, patients are seen for genetic consultation at the Maryland School for the Blind. This experience has resulted in the recruitment of patients into Clinical Branch protocols.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
ZO1 EY 00144-08 OGCSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)
Clinical Electrophysiology of the Vision

PRINCIPAL INVESTIGATOR (*List other professional personnel below the Principal Investigator.*) (*Name, title, laboratory, and institute affiliation.*)

PI:	Muriel I. Kaiser-Kupfer	M.D.	Chief, Ophthalmic Genetics and Clinical Services Branch	NEI
Others:	Rafael Caruso	M.D.	Visiting Scientist	OGCS, NEI
	T. Otis Paul	M.D.	Expert	OGCS, NEI
	Doris J. Collie	A.A.	Health Technician	OGCS, NEI

COOPERATING UNITS (*if any*)
Center for Sight, Georgetown University, Washington, DC (Despina Koustsandreas, B.S., Amy Pratt, C.O.T., Robert Toma, C.O.T.)

LAB/BRANCH
Ophthalmic Genetics and Clinical Services Branch

SECTION
Section on Ophthalmic Genetics

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.15	0.85	0.3

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (*Use standard unreduced type. Do not exceed the space provided.*)

The visual function of patients with ocular diseases or lesions in the visual pathways and of normal subjects is measured objectively with electrophysiological techniques. These data are correlated with those obtained with psychophysical tests of visual function. The results obtained contribute to the diagnosis of ocular and neural disorders that affect vision and are needed to characterize their nature and evolution. They are also valuable in the assessment of the effects of different forms of treatment on the outcome of these diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00172-07 OGCBS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Age Related Macular Degeneration

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Muriel I. Kaiser-Kupfer	M.D.	Chief, Ophthalmic Genetics and Clinical Services Branch	NEI
Others:	Monique S. Roy	M.D.	Visiting Scientist	CB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Ophthalmic Genetics and Clinical Services Branch

SECTION
Section on Ophthalmic Genetics

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.05	0.05	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This study will focus on patients with severe visual loss because of age-related macular degeneration in one eye who have good vision in the second eye. It will determine whether the good eye can be protected from severe visual loss by the administration of vitamin E and vitamin C when exposure of the retina to light below 500 nm is diminished. The recruited patients will be randomly assigned either to a treated or untreated control group and examined at 4-month intervals. Follow-up will continue for 5 years, unless an early beneficial or detrimental effect causes the study to be terminated in less than 5 years.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00211-04 OGCSB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)

A Double-Masked Controlled Randomized Clinical Trial of Topical Cysteamine

PRINCIPAL INVESTIGATOR (*List other professional personnel below the Principal Investigator.*) (*Name, title, laboratory, and institute affiliation.*)

PI:	Muriel I. Kaiser-Kupfer	M.D.	Chief, Ophthalmic Genetics and Clinical Services Branch	NEI
Others:	Lessie McCain	R.N.	Clinical Technician	OGCS, NEI
	Manuel Datiles	M.D.	Visiting Scientist	OGCS, NEI

COOPERATING UNITS (*if any*)

Human Genetics Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD (William Gahl, M.D., Ph.D.)

LAB/BRANCH

Ophthalmic Genetics and Clinical Services Branch

SECTION

Section on Ophthalmic Genetics

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.25	0.15	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (*Use standard unreduced type. Do not exceed the space provided.*)

Nephropathic cystinosis is an autosomal, recessively inherited storage disease in which nonprotein cystine accumulates within cellular lysosomes due to a defect in lysosomal cystine transport. Ocular manifestations include photophobia crystal deposits in cornea, conjunctiva, and iris, and depigmentation of the retina. Systemic complications include the Fanconi syndrome and renal failure.

Eight years ago cysteamine, a free thiol which depletes cystine from cells, was introduced in the therapy of cystinotic patients. Although patients had improved growth and stabilized renal function, there was no noticeable effect on the accumulation of corneal crystals. Recent studies showed that corneal cells in tissue culture are readily depleted of cystine by the introduction of cysteamine, making feasible the use of topical ophthalmic cysteamine to circumvent the humoral route. After appropriate animal studies to test for complications, which revealed none, we began a double-masked clinical trial to test the efficacy of topical cysteamine (0.1%) in humans. Twelve young patients have thus far been enrolled. Seven patients have shown significant decrease in crystals in the cysteamine-treated eyes and are now taking drops in both eyes. Furthermore, the study has been expanded to include older patients. Preliminary findings in one of eight patients are very exciting in that crystals have diminished and symptoms have been relieved. To test the effect of increasing the concentration of cysteamine eye drops in humans, a study was performed in rabbits. The results permit an increase in the concentration to 0.5% for human use.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 EY 00246-02 OGCSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)
Molecular Genetics of Retinal Degenerations

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)*

PI:	Michael B. Gorin	M.D., Ph.D.	Medical Officer	OGCS, NEI
Others:	Tatiana Putilina	Ph.D.	Staff Fellow	OGCS, NEI
	Ignacius Rodriguez	Ph.D.	Staff Fellow	OGCS, NEI

COOPERATING UNITS *(if any)*
Retinitis Pigmentosa Foundation, Northwestern University (Larry Pinto, Ph.D.), University of Linkoping, Linkoping, Sweden (Kristina Narfstrom, V.M.D.), Department of Biochemistry, UCLA (David Sigman, Ph.D.), Laboratory of Molecular Microbiology, National Institute of Allergy and Infectious Disease (Christine Kozak, Ph.D.)

LAB/BRANCH
Ophthalmic Genetics and Clinical Services Branch

SECTION
Section on Ophthalmic Genetics

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.8	1.8	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to identify the genes responsible for different inherited retinal disorders in animal models and to establish the genetic relationship of these animal disorders to forms of human retinal degenerations and other conditions.

"Reverse" genetic approaches are being applied to specific animal models of retinal dysfunction, including new methods for cloning regions associated with a mapped genetic disorder. Polymerase chain amplification methods are being used to evaluate interspecies differences in specific genetic transcripts. Genomic DNA is prepared for leukocyte nuclei of patients and appropriate family members with specific genetic retinal conditions. Linkage analysis of these samples uses random probes or candidate genes.